Amended Safety Assessment of
Salicylic Acid and Salicylates as Used in Cosmetics

Status: Final Amended Report
Release Date: June 5, 2019
Panel Date: April 8-9, 2019

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of Salicylic Acid and 17 salicylates; 15 of these ingredients were previously reviewed by the Panel, and 3 are reviewed herein for the first time. Some of the reported functions in cosmetics for ingredients in this group are hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients. Upon review of relevant new data, including frequency and concentration of use, and consideration of data from the previous CIR report, the Panel concluded that Salicylic Acid and 17 salicylate ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.[1] Based on the available data, the Panel issued the following conclusion: Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate; Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate; and Tridecyl Salicylate, and the esters Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection. Additionally, in 2015, the Panel published a safety assessment of MEA-Salicylate (as well as ethanolamine and other ethanolamine salts), and concluded that MEA-Salicylate, and the other ingredients named in the report, are safe in the present practices of use and concentration described in the safety assessment (rinse-off products only) when formulated to be nonirritating.[2] The Panel cautioned that this ingredient should not be used in cosmetic products in which *N*-nitroso compounds may be formed. The complete reports are available on the CIR website (https://www.cir-safety.org/ingredients).

In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. The Panel determined that the original conclusion should be reconsidered; therefore, a re-review was completed. Because MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts, it is not included in this re-review. Also, it was determined that Capryloyl Salicylic Acid is structurally and chemically dissimilar. Capryloyl Salicylic Acid was defined as an ester at the time of the original review; this was a mistake that has since been corrected. Based on the correct structure, it was determined that Capryloyl Salicylic Acid does not belong in this report.

The following ingredients, in addition to those included in the original report, are included in this safety assessment: Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. These 3 ingredients are esters of Salicylic Acid, and are structurally similar to the ingredients that were reviewed in the original report. The expanded list of 18 ingredients (15 of 17 from the original Final Report + 3 additions) appears below:

Butyloctyl Salicylate	Potassium Salicylate
Calcium Salicylate	Salicylic Acid
C12-15 Alkyl Salicylate	Sodium Salicylate
Ethylhexyl Salicylate	TEA-Salicylate
Hexyldodecyl Salicylate	Tridecyl Salicylate
Isocetyl Salicylate	
Isodecyl Salicylate	Amyl Salicylate
Magnesium Salicylate	Hexyl Salicylate
Methyl Salicylate	Isotridecyl Salicylate
Myristyl Salicylate	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), some of the functions in cosmetics that are reported for this group of salicylates include hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients.[3] The complete list of functions is presented in Table 1.

The published data in this re-review document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the 2003 report are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information, except for chemical and physical properties, is not included in the tables or the Summary section.)

Chemical registration dossiers submitted to the European Chemicals Agency, in conformity with the European Union's (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, are available for the following ingredients: Butyloctyl Salicylate, Ethylhexyl Salicylate, Methyl Salicylate, Salicylic Acid, and Sodium Salicylate. Some of the safety test data identified in REACH dossiers are included in the CIR final report on Salicylic Acid and 16 salicylates that was published in 2003. However, it should be noted that data from Salicylic Acid and salicylate REACH dossiers that became available subsequent to this final report publication are included in this report. This CIR report also contains data that are summarized in the 2018 Scientific Committee on Consumer Safety (SCCS) opinion on Salicylic Acid,[4] and in a 2002 opinion by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP).[5]

CHEMISTRY

Definition and General Characterization

Salicylic Acid (Figure 1), an aromatic monohydroxybenzoic acid (specifically, 2-hydroxybenzoic acid) is a colorless, crystalline organic acid that can be derived from salicin (a β-glucoside in willow bark).[6] The rest of the ingredients in this report (salicylates) are esters or salts of Salicylic Acid (Figure 2). The definitions of the salicylates reviewed in this safety assessment are included in Table 1.
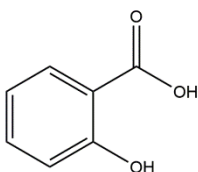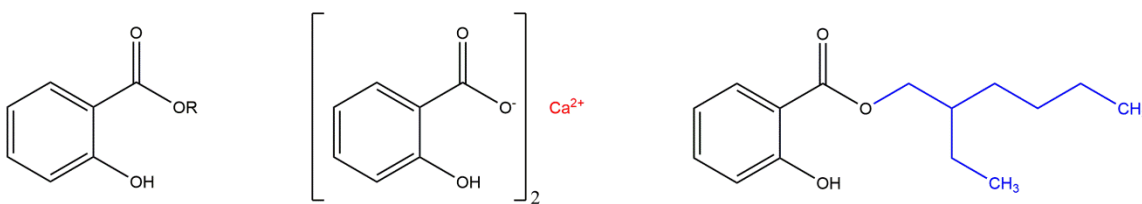

Figure 1. Salicylic Acid

Figure 2. Salicylates generic structure (wherein R is a salt cation or an alcohol residue), and examples: Calcium Salicylate and Ethylhexyl Salicylate, respectively.

Chemical and Physical Properties

The molecular weight of Salicylic Acid is 138 Da; its corresponding salts have formula weights from 160 to 298 Da. The acid and salts are solids at standard temperature and pressure (STP). The molecular weights are as small as 152 Da, and go up to 390 Da. These esters are liquids at STP and are acidic due to the phenolic hydroxyl group. The chemical and physical properties of Salicylic Acid and salicylates (salts and esters) are presented in Table 2.[7-12]

Method of Manufacture

Amyl Salicylate

Amyl Salicylate can be synthesized by heating a mixture of Salicylic Acid, *n*-amyl alcohol, and concentrated sulfuric acid under a reflux condenser for approximately 4 h.[13] After the unreacted alcohol has been removed by distillation at atmospheric pressure, the residue is washed with 10% aqueous potassium carbonate and dissolved in ether, and the ether

solution is dried over anhydrous sodium sulfate. The high-boiling material that remains after removal of the ether is fractionated under reduced pressure. The Amyl Salicylate fraction boils at 116 to 121ºC and 1.4 mm Hg. According to another source, Amyl Salicylate can be synthesized from Salicylic Acid and *n*-amyl alcohol, using sodium hydrogen sulfate as a catalyst.[14]

Impurities

Magnesium Salicylate

According to the *United States Pharmacopoeia* (*USP*), Magnesium Salicylate contains not less than 98% of this ingredient, and 0.004% heavy metals.[15]

Methyl Salicylate

According to the *National Formulary* (*NF*), Methyl Salicylate contains not less than 98% of this ingredient, and contains heavy metals up to 0.002%.[16]

Salicylic Acid

The *USP* specifies that Salicylic Acid contains not less than 99.5% of this ingredient, calculated on the dried basis.[15] The limit on phenol content is not more than 0.02%, and the limit on total impurities is not more than 0.2%.

Sodium Salicylate

According to the *USP*, Sodium Salicylate contains not less than 99.5% of this ingredient, calculated on an anhydrous basis, and not more than 0.0002% heavy metals.[15]

USE
Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.[17] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

The greatest use frequency of 3974 uses is reported for Ethylhexyl Salicylate, followed by 1429 reported uses for Salicylic Acid.[17] (Reported use frequencies for the remaining ingredients are ≤ 186.) The frequency of use for both of these ingredients increased greatly when 2019 VCRP data are compared to the VCRP data from the original report; in 1998, Ethylhexyl Salicylate was reported to have 83 uses and Salicylic Acid was reported to have 107 uses. Furthermore, in 1998, there were no reported uses of Magnesium Salicylate, but 11 uses are being reported in 2019.

The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration for leave-on formulations that is being reported for the salicylates that are reviewed in this safety assessment.[18] Salicylic Acid is being used at concentrations up to 30% in rinse-off products (peels); this is the highest maximum ingredient use concentration that is being reported for rinse-off products. In the published CIR final report on salicylates, the highest ingredient use concentrations in rinse-off and leave-on products were 3% (Salicylic Acid) and 8% (Ethylhexyl Salicylate), respectively.[1] Further use frequency and concentration of use data are presented in Table 3.

Collectively, according to 2019 VCRP data and the results from a 2018 Council use concentration survey, the following salicylates are not reported to be in use in cosmetic products in the US:

Calcium Salicylate
C12-15 Alkyl Salicylate
Hexyldodecyl Salicylate
Isocetyl Salicylate (was used at 3 - 5% in 2000;
    VCRP data were not reported at that time)

Isotridecyl Salicylate
Myristyl Salicylate
Potassium Salicylate

Cosmetic products containing salicylates may be applied to the skin (e.g., Salicylic Acid, up to 30% in peels) or, incidentally, may come in contact with the eyes (e.g., Ethylhexyl Salicylate, up to 0.1% in eye lotions).   These ingredients are also applied to mucous membranes and could be incidentally ingested (e.g., Butyloctyl Salicylate, up to 35.9% in lipsticks).   Products containing salicylates may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

The highest maximum ingredient use concentration in a spray product is being reported for Ethylhexyl Salicylate, which is used in suntan aerosol and pump sprays at concentrations up to 5%. The use concentration data on Ethylhexyl Salicylate in spray products relate to cosmetic ingredient functions other than that of a sunscreen; sunscreens are considered over-the-counter (OTC) drugs in the United States (21 CFR 352.10). Salicylic Acid is being used in suntan product pump sprays at concentrations up to 0.5%.   In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm, compared with pump sprays.[19,20,21,22] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[19,20] The highest maximum ingredient use concentration in a powder is being reported for Butyloctyl Salicylate, which is being used at concentrations up to 3.6% in face powders. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[23,24,25]

According to the EU's list of preservatives allowed in cosmetic products, a maximum use concentration of 0.5% (acid) was established for the following ingredients for use as preservatives in ready-for-use cosmetic preparations: Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, Sodium Salicylate, Potassium Salicylate, and TEA-Salicylate.[26] The following qualification relating to their use in cosmetics accompanies this concentration limit: Not to be used in products for children under 3 years of age, except for shampoos; this warning is associated with the use of these ingredients as preservatives, and applies to products which might be used for children under 3 years of age and which remain in prolonged contact with the skin. [For use other than as a preservative, See Annex III, No. 98].

Salicylic Acid is also included on the EU's list of substances which cosmetic products must not contain, except with the following restrictions: Maximum use concentrations in ready-for-use cosmetic preparations of 3% in rinse-off hair products and 2% in other products.[26]   This restriction applies to the use of Salicylic Acid for purposes other than inhibiting the development of microorganisms in the product; this purpose has to be apparent from the presentation of the product. Additionally, wording of conditions of use and warnings state not to be used in products for children under 3 years of age; this is solely for products which might be used for children under 3 years of age and which remain in prolonged contact with the skin.

An SCCS 2018 Final Opinion on Salicylic Acid supports the EU's concentration limits that are stated above.[4] It found that Salicylic Acid is safe when used as preservative at a concentration of 0.5 % in cosmetic products, with the current restrictions as described.   For uses other than a preservative, the Opinion supported concentrations up to 3.0 % for cosmetic rinse-off hair products and up to 2.0 % for other products, taking into considering the restrictions given. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, Salicylic Acid is considered safe up to 0.5% only as preservative. Also, for both preservative and non-preservative use, the Opinion is not applicable to any oral products (such as toothpaste and mouthwash), with the exception of lipstick. Additionally, sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

The EU has also established a maximum use concentration of 5% for Ethylhexyl Salicylate (as a UV filter allowed in cosmetic products) in ready for use cosmetic preparations.[26]

The International Fragrance Association has established the following concentration limits (relative to sensitization potential) for Hexyl Salicylate in different categories of cosmetic products when utilized as a fragrance ingredient:[27]

1% (**Category 1**: lip products of all types [solid and liquid lipsticks, balms, clear, etc.]),

1.3% (**Category 2**: deodorants and antiperspirant products of all types, including any product with intended or reasonably forseeable use on the axillae or labeled as such [spray, stick, roll-on, underarm, deo-cologne, and body spray, etc.]),

5.3% (**Category 3**: hydroalcoholic products applied to recently shaved skin (includes after shave); eye products of all types [eye shadow, mascara, eyeliner, eye make-up, eye masks, eye pillows, etc.], including eye care; men's facial creams and balms; tampons; body creams, lotions, and oils; and body paint for children),

16% (**Category 4**: hydroalcoholic products applied to unshaved skin [includes aqueous based, alcoholic based, and hydroalcoholic), like cologne, eau de cologne, eau de parfum, or parfum; body sprays [including body mist] with no intended or reasonably foreseeable use on the axillae; hair styling aids and hair sprays of all types [pumps, aerosol sprays, etc.]; body creams, oils, and lotions; solid perfumes; fragrancing creams of all types [except baby creams and lotions]; ingredients of perfume kits; fragrance compounds for cosmetic kits; scent pads; foil packs; scent strips for hydroalcoholic products; foot care products; hair deodorant; and body paint [except those for children],

8.4% (**Category 5**: women's facial creams/facial make-up; hand cream; facial masks; baby powder and talc; hair permanent and other hair chemical treatments [e.g. relaxers], but not hair dyes; wipes or refreshing tissues for face, neck, hands, and body; hand sanitizers; and dry shampoo or waterless shampoo),

25.7% (**Category 6**: mouthwash, including breath sprays, and toothpaste),

2.7% (**Category 7**: intimate wipes and baby wipes),

2% (**Category 8**: make-up removers of all types [not including face cleansers]; hair styling aids (non-spray) of all types [mousse, gels, leave-in conditioners, etc.]; nail care; powders and talcs of all types [except baby powders and talcs]; and hair dyes),

and **5%** (**Category 9**: bar soap [toilet soap]; bath gels, foams, mousses, salts, oils and other products added to bathwater; body washes of all types [including baby washes] and shower gels of all types; conditioner [rinse-of]; all depilatories [including waxes for mechanical hair removal]; face cleansers of all types [washes, gels, scrubs, etc.]; facial tissues; feminine hygiene – pads; feminine hygiene – liners; fragranced face masks [not intended to be used as medical device]; liquid soap; shampoos of all types [including baby shampoos]; and shaving creams of all types [stick, gels, foams, etc.])

Non-Cosmetic

Ethylhexyl Salicylate

Ethylhexyl Salicylate is an active ingredient, at the specified concentration of up to 5%, in OTC sunscreen drug products, whereby the finished product provides a minimum SPF value of not less than 2 [21 CFR 352.50]. When used as a sunscreen, this ingredient must be listed on the label as octisalate (which is the International Nonproprietary Name).

Methyl Salicylate

Non-aspirin salicylates (i.e., not acetylsalicylic acid), such as Methyl Salicylate, are found in many OTC brands of creams, ointments, lotions, liniments and medicated oils intended for topical application to relieve musculoskeletal aches and pains.[28]

Salicylic Acid

Salicylic Acid is a non-steroidal anti-inflammatory drug (NSAID), of which aspirin is a simple phenolic acetate derivative.[29] The FDA has issued a final rule for OTC drug products that permits the use of Salicylic Acid, at concentrations of 0.5 to 2%, as an active ingredient in topical acne drug products. [21 CFR 333.310]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Salicylic Acid and Methyl Salicylate

In vitro skin penetration data indicate that Salicylic Acid was percutaneously absorbed through pig, mouse, and rat skin and that Methyl Salicylate was percutaneously absorbed through pig and guinea pig skin.[1]

Ethylhexyl Salicylate and Salicylic Acid

A skin penetration study on Ethylhexyl Salicylate was carried out using human female abdominal skin (full-thickness skin obtained at autopsy) in Franz diffusion cells.[30] The receptor fluid was phosphate buffered saline containing 6% (w/v) oleth-20. When [^{14}C]-Ethylhexyl Salicylate (labeled on salicylate portion; 5% in oil-in-water; target dose = 5 mg/cm^2) was applied as a finite dose, the average total absorption of radioisotope over 48 h was 0.65 ± 0.16% of the applied dose. This value represented a total flux of 1.58 ± 0.36 µg/cm^2. When applied as a finite dose in a representative hydroalcoholic formulation containing 5% Ethylhexyl Salicylate, the average total absorption of radioisotope over 48 h was 0.59 ± 0.09% of the applied dose. This value represented a total flux of 1.58 ± 0.25 µg/cm^2. The penetration of Salicylic Acid was also determined in this study. When [^{14}C]-Salicylic Acid (in oil-in-water emulsion) was applied as a finite dose, the average total absorption of radioisotope over 48 h was 1.14 ± 0.23% of the applied dose. This represented a total flux of 1.65 ± 0.39 µg/cm^2. The authors noted that the data obtained in this study suggest that the in vitro human skin permeation of Ethylhexyl Salicylate is relatively low. They also noted that, using similar vehicles, the flux of Salicylic Acid was similar to that of Ethylhexyl Salicylate over a 48-h period. The authors also offered the supposition that the [^{14}C]-label appearing in the receptor fluid may, in both cases, represent salicylic acid, giving rise to the possibility that the amount of Ethylhexyl Salicylate permeating through the skin is much less than suggested by the data.

Ethylhexyl Salicylate

The skin penetration of a sunscreen formulation containing 5% Ethylhexyl Salicylate was evaluated using human full-thickness skin (from 3 women) that was mounted in a Franz diffusion cell with a receptor volume of 12.4 mL.[31] The sunscreen formulation tested was either in an oil-in-water emulsion gel or in petrolatum. The receptor compartment was filled with an aqueous solution containing sodium chloride (0.9%) and bovine serum albumin (1.5%). The cell allowed skin (1.76 cm^2) to be exposed to the sunscreen formulation, and the formulation (3.0 ± 0.4 µg/cm^2) was applied to the skin for either 30 min or 6 h. Each value for skin penetration is reported as the mean value (n = 4). After either duration, Ethylhexyl Salicylate was not detected in the dermis. Skin penetration and the amount of Ethylhexyl Salicylate found in the epidermis were the same following the 30-min application using both vehicles and the 6-h application using the oil-in-water emulsion gel; skin penetration was 0.4 µg/cm^2, and 0.2% of the applied dose was detected in the epidermis. The 6-h value for skin penetration of Ethylhexyl Salicylate (in petrolatum) into the epidermis was 0.6 µg/cm^2, and 0.3% of the applied dose was detected in the epidermis.

Methyl Salicylate

The skin penetration of Methyl Salicylate was evaluated using rat full-thickness skin (cleared of excess subcutaneous tissue) from male Wistar rats.[32] The skin was cut into 15 x 15 mm pieces and mounted in Franz-type glass diffusion cells (surface area = 1.3 cm^2). The receptor fluid consisted of degassed, 20% ethanol:80% distilled water. A formulation containing 20% Methyl Salicylate (1 g) was placed on the skin and receptor fluid was removed and replaced during the experiment. Approximately 25% of the Methyl Salicylate that was absorbed through the skin was hydrolyzed to salicylate. At 24 h, the total amount of salicylate that penetrated through the skin was < 20%.

In vitro skin penetration tests on Methyl Salicylate were performed using fresh dermatomed (0.3 to 0.4 mm thick) female breast skin and leg skin in Bronaugh flow-through polytetrafluoroethylene diffusion cells.[33] Each dose of the test substance was applied to a 0.38-cm^2 skin area in each cell. The receptor fluid was Hank's HEPES buffered saline with 4% bovine serum albumin (pH of 7.4). Skin samples were exposed to Methyl Salicylate for 30 min, and there was a 6.5 h reservoir collection period. The skin penetration of Methyl Salicylate was described as rapid. There was 32% absorption at the low dose (2 mM Methyl Salicylate), 17% absorption at the medium dose (20 mM Methyl Salicylate), and 11% absorption at the high dose (200 mM Methyl Salicylate). Regarding these results, the authors noted that the percent absorption from a high concentration of test chemical may be lower than that observed from a lower dose level, but may still give rise to higher calculated µg/cm^2/h amounts absorbed.

Percutaneous absorption of Methyl Salicylate was evaluated in the isolated perfused porcine skin flap (IPPSF).[34,35] A dose of 400 µg/cm^2 of radiolabeled [^{14}C]-Methyl Salicylate was applied non-occluded to a 7.5 cm^2 Stomadhesive® dosing template on the IPPSF. Skin flaps were allowed to equilibrate for 1 h prior to chemical application. A total of 16 flaps were dosed and terminated at 2, 4, or 8 h. Percutaneous absorption into IPPSF was 2.39% of the applied dose at 8 h. With the amount in skin and fat added, the penetration was 3.04% of the applied dose. The rate of absorption was also evaluated. Radiolabeled Methyl Salicylate showed a rapid absorptive flux profile that peaked at approximately 30 min at 0.016% dose/min.

The ester cleavage of Methyl Salicylate to Salicylic Acid in hairless mouse skin, in vitro, following topical application of 1% Methyl Salicylate in acetate buffer to the skin was evaluated.[36] At 5 h or 10 h, less than 5% of the applied dose was metabolized to Salicylic Acid.

Salicylic Acid

The in vitro percutaneous absorption of Salicylic Acid was evaluated using Franz diffusion cells and porcine skin dermatomed to a thickness of 500 ± 50 µm.[4] The receptor fluid consisted of phosphate-buffered saline, distilled water, bovine serum albumin, and gentamicin sulfate. An ethanol-water (1:1) solution containing Salicylic Acid (~ 3% w/v) was applied for 24 h to the entire skin surface. Treated stratum corneum was removed by 8 successive tape strippings, after which the dermis was separated from the epidermis. The different compartments for each active principle were analyzed using high-performance liquid chromatography. Dermal absorption of Salicylic Acid (epidermis, dermis, and receptor fluid) on intact skin was found to be $34.48\% \pm 2.56$ (n = 6). Total recovery was $99.28\% \pm 4.31$.

In another in vitro study, [14C]-Salicylic Acid (in ethanol) was applied to porcine skin (dermatomed to a thickness of 500 µm) using a flow-through porcine skin diffusion system.[4] Each square section (1 cm^2) of skin was placed in a two-compartment flow-through diffusion cell, to which [14C]-Salicylic Acid (in ethanol) was applied for 24 h. The dermal side of the skin sections was perfused using receptor fluid consisting of a Krebs-Ringer bicarbonate buffer spiked with dextrose and bovine serum albumin. The flow rate of the receptor solution was 4 mL/h. The treated area of skin was removed by 6 successive tape strippings, and samples were analyzed using a liquid scintillation counter. The dermal absorption of [14C]-Salicylic Acid in ethanol was 40.05% ($\pm 7.63\%$; n = 3).

The in vitro percutaneous absorption of [14C]-Salicylic Acid (2% in ethanol:water vehicle; dose = 40 µg/cm^2) was evaluated using human abdominal skin samples (split-thickness).[4] There were 12 skin samples from 4 different donors. The skin was dermatomed to a thickness of 200 to 400 µm, and the surface area of exposed skin within the diffusion cells was 3.14 cm^2. The receptor fluid consisted of phosphate-buffered saline, newborn calf serum, amphotericin B, penicillin, and streptomycin. Topical application involved an exposure period of 24 h. The results of this study provided a high-end estimate of skin absorption (worst case) of 50.09% (± 5.26).

A single dose of [14C]-Salicylic Acid was applied to dermatomed human skin (from cadaver) in vitro using Franz diffusion cell. The test substance (dose = 5 µl) was applied to skin under non-occlusion as well as various occlusive time periods (1 h, 4 h, and 8 h).[4] The receptor fluid consisted of phosphate-buffered saline. After 24 h, skin samples were removed and skin surface sites were tape-striped 10 times. Radioactivity in the epidermis and dermis represented the dose absorbed in the skin. The total amount of [14C]-Salicylic Acid absorbed in the skin (epidermis + dermis + receptor fluid) as a percent of the applied dose increased from 4.5% under non-occlusion to 50.5% when under 8 h of occlusion.

Animal

Salicylic Acid, Methyl Salicylate,
Sodium Salicylate, TEA Salicylate

In vivo percutaneous absorption data on rabbits (Salicylic Acid, Sodium Salicylate, and TEA Salicylate), guinea pigs (Salicylic Acid), rats (Methyl Salicylate, Salicylic Acid, and TEA Salicylate), dogs (TEA Salicylate), pigs (TEA Salicylate), and monkeys (Salicylic Acid), are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Methyl Salicylate

Twenty-seven 10-week-old Yorkshire-Landrace cross barrow pigs were used in a skin absorption study.[37] A circular plastic cup with two holes pierced through it to accept an 18-gauge needle was positioned over a piece of gauze cloth that was cut to a diameter slightly smaller than the cup, and that was placed over the skin. Four sites were challenged including ear, epigastrium, perineum, and inguinal crease with total area of exposure of 49.3, 132.4, 49.3, and 88.2 cm^2, respectively. Neat Methyl Salicylate was introduced into the cup through one of the holes at volumes of 848 µL for the ear, 2544 µl for the epigastrium, 848 µl for the perineum and 1696 µl for the inguinal crease. Arterial blood samples were taken every 10 min for the first 60 min and then every 15 min up to 360 min. The average dose absorbed through the skin at the ear region after 6 h was 11 µg/cm^2; at the perineum regions, the average dose absorbed was 8 µg/cm^2, and, through the epigastrium and inguinal crease regions, the average dose absorbed was 3 µg/cm^2. The initial flux (permeation rate) of Salicylic Acid through the skin after application of neat Methyl Salicylate was 0.063 µg/cm^2/min at the ear region, 0.025 µg/cm^2/min at the epigastrium region, 0.044µg/cm^2/min at the perineum region and 0.012 µg/cm^2/min at the inguinal crease region.

Human

**Salicylic Acid, Ethylhexyl Salicylate,
and Sodium Salicylate**

Data describing the penetration of salicylates through human skin are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Ethylhexyl Salicylate

The skin penetration of two Ethylhexyl Salicylate sunscreen formulations was evaluated in a study involving 6 subjects.[31] Penetration was determined by tape-stripping. Each sunscreen formulation was applied to 2 cm x 2 cm areas on the volar side of the forearm. At 30 minutes post-application, the remaining product formulation was removed from the skin using cotton swabs, and the skin was tape-stripped 16 times. The mean value (6 subjects) for penetration of Ethylhexyl Salicylate in oil-in-water emulsion gel into the stratum corneum was 28.4 ± 6.6 $\mu g/cm^2$, which corresponds to penetration of 25.6% of the applied dose into the stratum corneum. The mean value for penetration of Ethylhexyl Salicylate in petrolatum was 10.1 ± 3.5 $\mu g/cm^2$, indicating that 11% of the applied dose penetrated into the stratum corneum. The authors noted that the concentration of Ethylhexyl Salicylate in the upper part of the stratum corneum was significantly higher (p-value not stated) after application of the emulsion gel formulation than after application of the petrolatum formulation. In the deeper parts of the stratum corneum, the concentration of Ethylhexyl Salicylate delivered form the emulsion gel formulation was significantly lower (p value not stated) than that achieved with the petrolatum formulation.

The systemic absorption of a sunscreen lotion, with the following composition, after dermal application was evaluated using 9 healthy volunteers: Ethylhexyl Salicylate (5% w/v), oxybenzone (6% w/v), octocrylene (7% w/v), and octyl methoxycinnamate (7.5% w/v).[38] All of these chemicals were identified as sun screening agents. The subjects were instructed to apply the product to the entire surface of their forearms generously in accordance with their normal sun protection behavior. In practice, 13.0 ± 1.0 g [mean and standard error of the mean values, respectively] of sunscreen product was applied to a surface area of 1051 ± 60.8 cm^2. The application density of the product was 12.4 mg/cm^2. The formulation remained unoccluded for 12 h prior to removal with soap and water. Urine samples were collected before product application and at 48 h post-application. Over the period of application, only 1 to 2% of the sunscreen in the applied product was absorbed and subsequently excreted in the urine. Urine samples were analyzed using high performance liquid chromatography. Data comparing the absorption of each ingredient were not provided.

Methyl Salicylate

The systemic exposure to Methyl Salicylate following the application of a number of adhesive patches (each containing 74.88 mg Methyl Salicylate) to the skin of 8 human subjects was evaluated.[39] The patches remained in place for 8 h. Blood samples were obtained for up to 12 h after placement of the patches. Exposure was quantified by determining the plasma concentration time profiles of the substance as a function of exposure to 2 patches (normal doses), 4 patches, or 8 patches (very high doses).   Data were presented as a plot of the average plasma concentration-time data as a function of dose. For the 2-patch application, the average maximum plasma concentration (C_{max}) value for Methyl Salicylate was 8.6 ± 3.8 ng/mL (range: 4.0 - 12.7 ng/mL). For the 4-patch application, the average C_{max} for Methyl Salicylate was 16.8 ± 6.8 ng/mL (range: 8.9 - 25.7 ng/mL). For the 8-patch application, the average C_{max} was 29.5 ± 10.5 ng/mL (range: 15.8 - 45.9 ng/mL). The authors noted that although it was not possible to determine the absolute dermal bioavailability of Methyl Salicylate, there appeared to be relatively low systemic exposure, even when an unrealistically large number of patches were applied for an unusually long time.

Computational

**Ethylhexyl Salicylate, Hexyl Salicylate,
and Methyl Salicylate**

A mathematical method was used to estimate total body absorption of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate. Rate constants were calculated from the relevant physicochemical properties.[40] The applied dose of each ingredient used in the simulation was 40 $\mu g/cm^2$ based on the FDA recommendation (200 mg of product per 100 cm^2 of skin) and a value of 2% active ingredient in the formulation. The release rate from the formulation was fixed at 1 $\mu m/cm^2/h$. The simulations were conducted on a 12-h time scale. The estimated total body absorption values (skin area) for each ingredient were: 0.022 $\mu g/1.4$ m^2 at 2 h, 0.50 $\mu g/1.4$ m^2 at 6 h, and 3.3 $\mu g/1.4$ m^2 at 12 h (Ethylhexyl Salicylate); 0.18 $\mu g/1.4$ m^2 at 2 h,

4.1 µg/1.4 m^2 at 6 h, and 27 µg/1.4 m^2 at 12 h (Hexyl Salicylate); and 91 µg/1.4 m^2 at 2 h, 2000 µg/1.4 m^2 at 6 h, and 13,000 µg/1.4 m^2 at 12 h (Methyl Salicylate). It should be noted that 1.4 $m^2 \approx$ 75% of the total average area of human skin.

Penetration Enhancement

Salicylic Acid

Salicylic Acid is reported to enhance percutaneous penetration of vitamin A, ammoniated mercury, and triamcinolone acetonide, but not methyl nicotinate, (which itself rapidly penetrates the skin), hydrocortisone, diflucortolone-21-valerate, or cyclosporine.[1]

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Placental

The placental absorption of Salicylic Acid was studied in vitro in an effort to devise a pharmacokinetic model of human placental absorption.[41] Salicylic Acid (8 µg/mL) was dissolved into the maternal perfusate on the maternal side of the placenta. Maternal- and fetal-side effluents were sampled for 60 min. Study results indicated the potential for Salicylic Acid to cross the placenta.

Animal

Dermal

Methyl Salicylate

The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using groups of 3 male Wistar rats.[32] The formulation (1 g) was applied to a 9.6 cm^2 area of abdominal skin, and a blood sample was removed from the tail vein at 0.5, 1, 2, 4, and 6 h thereafter. After blood removal at each time point, the animals (3 per time point) were killed, the formulation was removed from the skin, and tissue samples (skin, subcutaneous tissue, superficial muscle, deep muscle, and fat) were excised. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/mL throughout the study period. The highest concentrations were observed in the dermal and subcutaneous sites in the first hour of application. At 0.5 to 1 h after application of the formulation, there was a significant increase in the concentration of total salicylate in contralateral dermal tissue, corresponding to 4 to 5 times above the circulating systemic plasma levels. At 2 h, the dermal levels were below the observed plasma salicylate concentration. The presence of unhydrolyzed Methyl Salicylate was only observed at the 0.5 h time point. The fraction of Methyl Salicylate observed in the tissues as a proportion of total salicylate varied from 0 to 0.26. The results of this study indicate that tissue and plasma concentrations of salicylate after the application of Methyl Salicylate increased rapidly within the first hour of application.

Oral

Salicylates

Extensive data from oral delivery studies in animals are available.[1] *Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.*

Human

Oral

Salicylates

Extensive data from oral delivery human studies are available.[1] *Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.*

Methyl Salicylate

Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid.[28] No further details were provided.

Four (1 male/3 female) adult human volunteers participated in a study that was conducted as an open label, 4-way crossover design with randomized treatment order.[42] The subjects ingested 6.7 and 20 g of a Methyl Salicylate-containing cream (commercial 15% cream containing 900 or 2700 mg salicylate). Plasma was collected at 0, 20, 40, 60, 120, 240, 480, 720, and 1440 min for the determination of salicylate concentrations using the Abbott TDx® fluorescence polarization immunoassay. The times to reach maximum salicylate concentration (T_{max}) and the peak plasma salicylate concentration (Cp_{max}) were determined. The T_{max} for the low-dose cream (900 mg salicylate) was 2.4 h (1.5 - 4 h), and the Cp_{max} was 42 mg/l (36 - 51 mg/l). The T_{max} for the high-dose cream was 7 h (4 - 12 h), and the Cp_{max} was 145 mg/l (120 - 201 mg/l). As a part of the same experiment, four fasting adults ingested 1 mL of wintergreen oil (which is primarily Methyl Salicylate; 14.2 mg/kg mean). Plasma was collected for salicylate determination at 0, 20, 40, 60, 120, 240, 480, 720, and 1440 min. Time to reach maximum concentration was 2.4 h with the maximum concentration of 70 mg/l. The 4 subjects were also instructed to hold 5 g of the cream in the buccal cavity for 1 minute and then expectorate. No plasma salicylate was detected after the buccal treatment phase.

Salicylic Acid

After oral administration to humans, Salicylic Acid is found in unionized form in the stomach.[4] It is well absorbed from the gastrointestinal tract and is rapidly distributed throughout the extracellular fluid and most tissues. High concentrations (not specified) are found in the liver and kidneys and 50% to 80% of Salicylic Acid in the plasma is bound to albumin and other proteins.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Acute dermal LD_{50}s of > 2 g/kg were reported when rats were exposed dermally to Butyloctyl Salicylate, Methyl Salicylate, Salicylic Acid, and Tridecyl Salicylate.[1]

Ethylhexyl Salicylate

Undiluted Ethylhexyl Salicylate was applied (under occlusion) to intact or abraded skin of 4 rabbits for 24 h.[7] The animals were observed for mortality and/or clinical signs for a 14-day period. No clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5.0 g/kg.

Hexyl Salicylate

Ten rabbits received a single dermal application of neat Hexyl Salicylate at 5.0 g/kg.[8] The rabbits were observed for mortality and clinical symptoms. No clinical signs were observed. The acute dermal LD_{50} in rabbits exceeded 5.0 g/kg based on 0/10 deaths at that dose.

Methyl Salicylate

A single dermal application of neat Methyl Salicylate at 5 g/kg was applied to 4 rabbits (strain not stated) for 24 h under occlusion.[7] Animals were observed for a 14-day period. None of the animals died, and no clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5 g/kg.

Salicylic Acid

In a study involving 3 New Zealand White rabbits, Salicylic Acid (0.5 g, moistened with 0.5 mL water) was applied, under a semi-occlusive patch, for 4 h to a 6.25 cm^2 area of skin. [4] The animals were observed for up to 14 days after application. None of the animals died, and there were no clinical signs of systemic toxicity during the study.

Sodium Salicylate

The acute dermal toxicity of Sodium Salicylate was evaluated using Wistar rats (5 males, 5 females).[43] The test substance (in 0.2 mL distilled water; dose = 2 g/kg) was applied to a dorsal area (~ 10% of body surface area) on the trunk, and the site was covered with an occlusive patch for 24 h. Dosing was followed by a 14-day observation period, after which the animals were killed. None of the animals died during the observation period. Clinical signs were described as normal throughout the study, and the results of both external and internal gross pathological examinations were not indicative of any pathological abnormality. The acute dermal LD_{50} was considered to be > 2 g/kg.

Oral

The following acute oral toxicity data for Salicylic Acid and salicylates have been reported in studies involving rats: Butyloctyl Salicylate (LD_{50} > 5 g/kg), Ethylhexyl Salicylate (LD_{50} > 2 g/kg), Isodecyl Salicylate (no toxicity at levels as high as 4.83 g/kg), Methyl Salicylate (LD_{50} between 0.887 g/kg and 1.25 g/kg), Salicylic Acid (LD_{50} ranging from 0.891 g/kg to 1.58 g/kg), Sodium Salicylate (LD_{50} between 0.9 g/kg and 1.7 g/kg); and Tridecyl Salicylate (LD_{50} > 1.98 g/kg).[1] Values for acute oral toxicity in other species are consistent with these values.

Ethylhexyl Salicylate

In an acute oral toxicity study involving 10 rats (strain not stated) dosed with Ethylhexyl Salicylate, the animals were observed for mortalities and/or clinical signs for 14 days post-dosing.[7] It was concluded that the acute oral LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 6 of the study. No clinical reactions were observed.

Hexyl Salicylate

The acute oral toxicity of Hexyl Salicylate was evaluated in a study involving 10 rats.[8] The rats were observed for mortalities and/or systemic effects for 14 day after dosing. Urinary incontinence was observed at 24 h. It was concluded that the LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 4 of the study.

Methyl Salicylate

The acute oral toxicity of Methyl Salicylate was determined in ddY male mice (10/dose).[44,9] Methyl Salicylate was administered at dose levels of 1.0, 1.2, 1.3, 1.5, or 1.7 g/kg. Mice were observed for a 7-day period. One animal died at 1.0 g/kg; 2/10 died at 1.2 g/kg; 4/10 died at 1.3 and 1.5 g/kg; and 9/10 died at 1.7 g/kg. Most animal deaths occurred on day 1. The LD_{50} was calculated to be 1.39 g/kg (95% CI 1.25 - 1.54 g/kg).

Methyl Salicylate was evaluated as a part of a study investigating the development of acute myocardiopathy in dogs.[45] Healthy mongrel dogs were lightly anesthetized with pentobarbital sodium. Methyl Salicylate was intragastrically administered at a dose of 0.7 g/kg. After 4 - 5 h, animals either died or were sacrificed. Increases in arterial concentrations of plasma salicylate, potassium and lactate were seen and a period of respiratory alkalosis was initially observed followed by metabolic acidosis after three hours. Microscopy studies revealed abnormalities in the mitochondria, swelling of cardiac muscles with separation of myofibrils and bulging of sarcolemma.

Salicylic Acid

A single dose of an aqueous solution of Salicylic Acid (in gum Arabic) was administered to 10 Wistar rats.[4] LD_{50} values in the range of 0.5 to 2 g/kg were reported.

Sodium Salicylate

The acute oral toxicity of Sodium Salicylate, in the diet, was evaluated using 6 Wistar rats.[43] Three animals (male/female) received a dose of 0.2 g/kg and another 3 animals (males) received a dose of 2 g/kg. All of the male rats dosed with 2 g/kg died, but there were no deaths at the lower dose. The mean lethal dose of Sodium Salicylate in male and female Wistar rats was considered to be > 0.2 g/kg to ≤ 2 g/kg.

Inhalation

Methyl Salicylate

The inhalation exposure of mice and rats to Methyl Salicylate (heated to 80°C) for an unknown duration did not cause death (LC$_{50}$ > 400 mg/m^3).[1]

Salicylic Acid

The acute inhalation toxicity of Salicylic Acid was evaluated using 6 male rats (strain not stated).[46] The animals were exposed for 1 h to Salicylic Acid as a dust (0.9 mg/l, in inhalation chamber). Data on particle size distribution were not reported. However, the authors noted that data from typical production batches indicate that less than 5% of particles are in the respirable range (mass mean aerodynamic diameter [MMAD] = < 4 μm). Median MMAD is in the range of 35 to 50 μm, with up to 20% non-inhalable particles of > 100 μm. Exposure was followed by a 14-day observation period and necropsy. The only signs observed were: salivation, nasal discharge, and lacrimation. No significant gross pathological changes were reported. The 1 h LC$_{50}$ was > 0.9 mg/l.

Short-Term Toxicity Studies

Dermal

Salicylic Acid

A 14-day dermal toxicity study was performed using groups of 6 (3 males, 3 females) New Zealand White rabbits.[5] The concentrations of Salicylic Acid (in 8% propylene glycol butyl ether in ethanol) tested were 2%, 10%, and 25% (corresponding to 40, 200, and 500 mg/kg/day, respectively). These concentrations were administered topically at a dose of 2 g/kg/day. The control group received topical applications of vehicle only. None of the animals died. Atonia was predominantly observed in the 10% and 25% Salicylic Acid groups. No remarkable changes in body weight were observed during the study. Results relating to visible changes in the skin are included in the section on Skin Irritation. Other than the observations relating to the skin, there were no visible abnormalities at necropsy.

Oral

Butyloctyl Salicylate

The short-term oral toxicity of a Butyloctyl Salicylate trade name material was evaluated according to the Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 407 using 3 groups of 5 albino Sprague-Dawley derived [Crl: CD BR] rats.[47] The 3 groups received the test substance (in corn oil, by gavage) at doses of 15, 150, and 1000 mg/kg/day, respectively, for 28 days. The animals were killed during week 4 (day 29). Mean prothrombin and activated partial thromboplastin times were increased in the 1000 mg/kg/day group. There were no test substance-related changes in the following in any dose group: body weights, food consumption, motor activity levels, functional observation batteries, organ weights, or macroscopic and microscopic pathology evaluations. The no-observed-effect level (NOEL) was considered to be 150 mg/kg/day dose.

Methyl Salicylate

Groups of 2 dogs (breed not stated) were dosed orally with Methyl Salicylate (in capsule form) at doses up to 1200 mg/kg daily (6 days per week) for up to 59 days.[1] Marked fatty changes in the liver were observed in both animals at the highest dose. No adverse effects were observed at doses of 50 to 250 mg/kg. Groups of 12 male and female rats (strain not stated) were fed diets containing methyl Salicylate at concentrations up to 12,000 ppm (i.e., 12,000 mg/kg) for 7 weeks. Bone lesions were observed at the highest dietary concentration only. In a shorter-duration study, that involved the feeding of 10 male rats with 12,000 ppm Methyl Salicylate in the diet for up to 5 days, bone lesions were not observed. However, when groups of 10 male and 10 female rats (strain not stated) were fed 12,000 ppm or 20,000 ppm Methyl Salicylate for 8 weeks, bone lesions were observed in all animals of both groups. Also, when groups of 5 male rats were fed 20,000 ppm Methyl Salicylate and a protein diet (75% basic feed and 25% casein) with water for 7 weeks, an increase in cancellous bone was reported. This finding was not reported in the group that was fed the same concentration of Methyl Salicylate plus the protein diet and 40% dextrose (dextrose, but no water). In a study that was longer in duration than the preceding 4 studies, groups of 10 male and 10 female Sprague-Dawley rats were fed a fat-enriched diet containing up to 2% Methyl Salicylate for 11 weeks. At the highest dietary concentration and the 1.2% concentration, but not at lower concentrations, bone lesions were observed at week 2; microscopic changes were observed at weeks 2 and 8 in these 2 groups, respectively. In another

11-week study, 5 male and 5 female rats were fed 12,000 ppm Methyl Salicylate and bone lesions were observed at 4 weeks (earliest time at which x-rays were taken). Decreased body weight was also observed in these studies.

The oral toxicity of Methyl Salicylate was determined in male and female CD-1 mice (8/sex/dose).[48] Methyl Salicylate was administered in corn oil by gavage once daily for 14 days at dose levels of 0.05, 0.1, 0.25, 0.50, and 1 g/kg. Two females died at 0.05 g/kg; 1female and 1 male died at 0.10 g/kg; and 2 females and 3 males died at 1 g/kg. Clinical signs observed prior to death were piloerection and dehydration. A probit analysis of the lethality data for the sexes combined projected an acute LD_{50} of 1.44 g/kg/day.

Salicylic Acid

In groups of rats dosed orally with Salicylic Acid (in distilled water, 500 mg/kg/day) for 3 days, hepatic and plasma parameters were determined 18 h after the last dose.[1] When compared to controls, a significant increase in each of the following was reported: aniline hydroxylase, glutathione, plasma aspartate aminotransferase (AST), and plasma alanine aminotransferase (ALT) activities, and a significant decrease in glucose-6-phosphatase activity.

Sodium Salicylate

Sodium Salicylate short-term oral exposures are linked with reduced growth and feed consumption, clear kidney damage, and some liver damage.[1] In these studies, rats received up to 21,020 ppm (i.e., 21,020 mg/kg) Sodium Salicylate in the diet for 11 weeks or up to 600 mg/kg of 10% aqueous Sodium Salicylate for 4 to 21 days. In the 21,020-ppm study, a positive increase in cancellous bone was observed. In one of the studies, in which groups of Fischer 344 rats were dosed orally with aqueous Sodium Salicylate for 4 weeks, the 28-day LD_{50} was 646.5 mg/kg. Liver and kidney necrosis was observed in dogs that received 300 mg/kg of 10% aqueous Sodium Salicylate for 2 weeks. A group of 6 male and 6 female Sprague-Dawley rats was fed a 5% hydrogenated fat-enriched diet containing 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% at week 11, and bone lesions were observed. Groups of 5 male Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.7% or 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% in the low-dose group at week 7 and in the high-dose group at week 2. Bone lesions were observed with 2.1% Sodium Salicylate.

Inhalation

Amyl Salicylate

The short-term inhalation toxicity of a fragrance mixture containing 5.8% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[49] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), 5 days per week (4 h per day) for 6 weeks (26 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 μm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

In a study involving 4 female Alderley Park rats, no toxicity was observed after inhalation of Methyl Salicylate in a series of 20 exposures of 7 h each at 0.7 g/m^3.[1] The organs appeared normal at necropsy.

Subchronic Toxicity Studies

Dermal

Methyl Salicylate

Subchronic dermal exposures to Methyl Salicylate were associated with kidney damage.[1] Groups of 3 rabbits were dosed dermally with synthetic Methyl Salicylate (doses up to 4 mL/kg) five days per week for up to 96 days.

Salicylic Acid

Two 91-day studies involving New Zealand White rabbits (number of animals used per study not stated) were performed to evaluate the cutaneous and systemic toxicity of 2 cleansing formulations containing 0.5% Salicylic Acid.[5] The

undiluted product or the product diluted to a concentration of 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) was applied. The test article (dose volume of 2 mL/kg; dose = 10 mg/kg) was applied (method not stated) to intact skin 5 times per week (7 h per day). Control rabbits were treated with distilled water. Both gross and histopathological examinations were performed. Results relating to skin reactions are included in the Skin Irritation section of this report. None of the animals died, and there were no statistically significant differences in mean body weight or organ weights during the study. Clinical evaluations as well as clinical chemistry, hematology, and histopathological examinations provided no evidence of systemic toxicity.

Another 91-day study involving New Zealand White rabbits (number not stated) was performed to evaluate the systemic and cutaneous toxicity of cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle).[5] This concentration range corresponded to topical doses of 10, 20, 40, or 120 mg/kg Salicylic Acid. Untreated and vehicle control groups were included in the study. The products tested were applied (method not stated) for 7 h to intact skin (once daily; dose volume = 2 mL/kg) 5 days per week. Five animals were killed after 28 days, and the remaining rabbits were killed at day 91. Serum salicylate (concentration not stated) was observed in all groups at 1 h post-dosing; the maximum serum levels were found between 2.5 h and 7 h after dosing. None of the animals died during the study, and there were no test substance-related changes in appearance, behavior, body weights, or ophthalmoscopic examinations. Slight to moderate atonia was also observed at the application site. There were no treatment-related effects on body weight gain or changes in body weight. Regarding hematological, biochemical, or urological parameters, there were no test substance-related toxicological findings. At histopathologic examination (day 91), a low incidence of trace to mild myocardial degeneration was observed in all dose groups and in the vehicle control group. However, there was no dose-response relationship for this finding. Results relating to skin irritation are included in the Skin Irritation section of this report.

Oral

Isodecyl Salicylate

No toxicity is seen with subchronic oral exposure to Isodecyl Salicylate.[1] Ten male and 10 female Wistar albino rats were fed 0.5% (~ 500 mg/kg/day) Isodecyl Salicylate in a basal diet for 15 weeks.

Methyl Salicylate

Subchronic oral exposure to Methyl Salicylate results in reduced weight gain and bone lesions, which disappear when Methyl Salicylate is co-administered with calcium carbonate.[1] All of the feeding studies involved rats, and the longest duration study involved groups of 20 Osborne-Mendel rats fed up to 1% synthetic Methyl Salicylate in the diet for 17 weeks.

Sodium Salicylate

The neurotoxic potential of 138 to 550 mg/kg Sodium Salicylate was determined using groups of 9 to 10 Fischer 344 rats dosed 5 days per week for 15 weeks.[1] The LD_{50} during 15 weeks of dosing was estimated to be 366.5 mg/kg; a dose-related decrease in hindlimb grip strength was noted.

Tridecyl Salicylate

Ten male and 10 female Wistar rats were fed ~500 mg/kg/day Tridecyl Salicylate in a basal diet for 15 weeks.[1] A control group of 10 males and 10 females was given untreated feed. There was no evidence of treatment-related effects. Oral administration of ~ 500 mg/kg/day Tridecyl Salicylate did not produce a significant toxic effect.

Inhalation

Amyl Salicylate

The subchronic inhalation toxicity of a fragrance mixture containing 4% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[49] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), 5 days per week (4 h per day) for 13 weeks (62 to 67 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 µm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in

hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

Male white rats (number per group not specified) were exposed to 1.2, 8, or 40 mg/m³ Methyl Salicylate for 4 months (4 h/day).[1] The highest concentration caused changes in nervous system function. Also, pulmonary focal hemorrhages and hyperplasia were observed in the peribronchial lymphoid tissue. Focal hemorrhages in the kidneys were observed.

Chronic Toxicity Studies

Oral

Methyl Salicylate

In the study with the highest administered dose, groups of 5 male and 5 female rats were fed a diet containing 2000, 3550, 6300, 11,250, or 20,000 ppm Methyl Salicylate for 30 weeks.[1] During weeks 1 and 2, Methyl Salicylate was given at 50%, and, during weeks 3 and 4, it was given at 75% of the final dose. At week 10, animals of the 11,250 ppm and 20,000 ppm groups had positive increased bone density in the femur and tibia. The largest 2-year feeding studies, involved groups of 50 rats fed up to 2% Methyl Salicylate in the diet. One of the 2 studies had no gross or microscopic findings. In the other study, statistically significant growth inhibition was observed in animals of the 1% and 2% dietary groups. Also, in the 1% dietary group, relative organ-to-body weight ratios for the testes (males) and for the heart and kidneys (females) were significantly increased. Gross lesions of the pituitary gland were observed in 10 animals of the 0.5% dietary group, compared to 4 animals in the control group. In the 2% dietary group, pneumonia was observed in 29 of the 50 animals. When groups of Beagle dogs received oral doses of Methyl Salicylate up to 350 mg/kg for 2 years (6 days per week), animals of the 150 and 350 mg/kg groups had retarded growth and enlarged livers. When Beagle dogs received oral doses of Methyl Salicylate up to 800 mg/kg/day for 6.6 to 7.5 months, an increase in liver and kidney weight was observed in treated animals, but the 150 and 300 mg/kg doses did not induce lesions or other deleterious alterations.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

Salicylic Acid

The effect of Salicylic Acid on human spermatozoa was determined after incubation with 50, 100, or 200 mg/l salicylate for 2 to 48 h.[1] A dose response effect was observed, with significant inhibition of motility at all time points.

Post-implantation day 11 rat embryos were cultured for 24 h with 10, 100, or 1000 μg/mL Salicylic Acid.[50] The growth and development of each embryo was evaluated and compared with control embryos for the presence of any malformations. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner, when compared with controls. However, exposure to Salicylic Acid at 10 μg/mL culture did not show any significant effect on embryonic growth and development. Parallel to this, flow cytometric analysis (cell cycle and annexin V binding) and DNA fragmentation assay were carried out followed via quantitation by 3′-OH labeling of cultured rat embryos to evaluate the role of apoptosis in bringing about Salicylic Acid-induced teratogenesis. All results were found to be dose-dependent and an increase in apoptosis in embryonic tissues may be related to the increased risk of congenital malformations. The data suggested that apoptosis might be involved in mediating teratogenesis of Salicylic Acid in vitro.

Salicylic Acid and Sodium Salicylate

The effects of Salicylic Acid and Sodium Salicylate on early organogenesis and the interaction of these chemicals with free radicals was investigated.[51] Post-implantation Wistar rat embryos were cultured in vitro from day 9.5 of gestation for 48 h; each test substance was added to whole rat serum at concentrations between 0.1 and 0.6 mg/mL. Also, each test substance (0.3 mg/mL) was added to the culture media in the presence of superoxide dismutase (30 enzyme units (U)/mL) or glutathione (0.5 μmol/mL). The growth and development of embryos was compared, and each embryo was evaluated for the presence of malformations. When compared to the growth of control embryos, both chemicals decreased all growth and developmental parameters in a concentration-responsive manner. There was also a concentration-related increase in overall dysmorphology, including the following: hematoma in the yolk sac and neural system, open neural tube, abnormal tail torsion, and the absence of forelimb bud. When superoxide dismutase was added in the presence of Salicylic Acid, the incidence of malformations was decreased. However, the addition of superoxide dismutase did not affect the growth and

developmental parameters of Salicylic Acid and Sodium Salicylate. The addition of glutathione significantly decreased the incidence of the malformations that were observed in the presence of Salicylic Acid. The authors noted that the effects of salicylates might involve free oxygen radicals by the non-enzymatic production of the highly teratogenic metabolites 2,3-dihydroxybenzoic acid and 2,5-dihydroxybenzoic acid. Furthermore, they noted that an enhanced production of these metabolites in embryonic tissues may be directly related to the increased risk of congenital malformations.

Animal

Dermal

Methyl Salicylate

Methyl Salicylate was applied (at 7 days 9 h of gestation) to dorsal skin of timed-pregnant LVG hamsters (number not stated), at doses of 350 and 525 mg/100 g.[1] *Few embryos from the high-dose group survived beyond 12 days of gestation, but, of the 19 litters produced in this group, there were 53% neural tube defects. Of the 6 litters produced in the lower dose group, 6% of the fetuses had neural tube defects. A peak salicylate level of 50 mg/100 mL was obtained 5 to 6 h after topical application of 350 mg/100 g and a peak of 120 mg/100 g with the 525 mg/100 g topical treatment level. Thus, dermal exposure to Methyl Salicylate is associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure.*

Oral

Ethylhexyl Salicylate

Because the following 2 study summaries (from different sources) involve the same strain of rats and doses, and 1 maternal death in the highest dose group is reported in both, it is possible that results from the same study are being reported. However, because a NOAEL is being reported in one study summary, and a NOEL in the other, and the dose corresponding to each is not the same, the results are being presented separately.

The developmental toxicity of an Ethylhexyl Salicylate trade name material was evaluated using groups of 11 RccHanTM: WIST(SPF) male and female rats.[47] The test substance (in corn oil) was administered by gavage to 3 groups at doses of 25, 80, and 250 mg/kg/day, respectively. The exposure (once daily exposure) periods for males and females were 28 days and ~ 7 weeks, respectively. Males were treated over a 14-day pre-pairing period and during the pairing period up to 1 day before necropsy. Females were treated throughout the pre-pairing, pairing, gestation and lactation periods up to day 3 post-partum. Maternal toxic effects were described as slight, but non-significant, changes in weight gain at a dose of 250 mg/kg/day. Because of the reduced absolute body weights of pups from the 250 mg/kg/day dose group, the NOEL for developmental toxicity was considered to be 80 mg/kg/day. No test substance-related microscopic findings were observed in pups from any of the dose groups. Another interpretation of data from the same study appears below.

In a developmental toxicity study that was performed according to the preceding test procedure (same doses, number of animals per group, and species), 1 maternal death (in highest dose group) that was unrelated to dosing with the same Ethylhexyl Salicylate trade name material was reported.[30] There were no further reports of adverse effects in males or females that were mated. In the 80 and 250 mg/kg/day dose groups, a reduction in the gestation index as well as an increased incidence of post-implantation loss (i.e., reduced litter sizes) were observed. These findings were dose-related as well as statistically significant, and were deemed test substance-related. No test substance-related effects were observed during the first litter check or during lactation in any of the dose groups. Dosing with the test substance also had no effect on pup sex ratio. A test substance-related effect on pup body weight (reduction in absolute body weight) was observed in the highest dose group. There were no test substance related effects (on body weight or body weight gain) in the 2 lower dose groups. Furthermore, no test substance-related macroscopic findings in pups were observed in any of the dose groups. Based on observations of increased post-implantation loss, reduction in the gestation index, and lower litter size, the no-observed-adverse-effect-level (NOAEL) for developmental toxicity was determined to be 25 mg/kg/day.

Methyl Salicylate

Methyl Salicylate was delivered by oral intubation (1.75 g/kg) to timed-pregnant LVG hamsters at 7 days 9 h of gestation.[1] *Blood levels reached a peak at of 125 mg/100 mL at approximately 2 h after oral dosing. Of 35 litters (number of fetuses per litter not given) in the treatment group, 72% of the fetuses had neural tube defects. Groups of 24 to 27 rats were fed 4000 ppm or 6000 ppm Methyl Salicylate in a test diet containing calcium carbonate for 60 days prior to mating and through weaning at day 20 or 21. This procedure was repeated. Abnormalities were not observed in offspring. Neonate survival at weaning was greater in the test group than in the control group. Groups of F_0 generation mice (25/sex/group) and F_{1b} generation mice (30 males and 30 females/group) received 0.25% or 0.5% Methyl Salicylate in feed for 30 days prior*

to mating. The results are only from females in each generation that mated twice. There was no evidence of gross abnormalities in any litter. All surviving neonates appeared normal, and no reproductive abnormalities were observed. Another experiment in the same study involved the same numbers of F_0 and F_{1b} animals (in this experiment, Wistar rats used) and the same concentrations of Methyl Salicylate administered in feed. The protocol was the same, except for the 60-day feeding period prior to mating. Gross abnormalities were not observed in any litter and all surviving neonates appeared normal. Mating performance and reproduction and viability indices were decreased, and the number of deaths between birth and day 5 were increased in the 0.5% group. Litter size was decreased in both test groups. Groups of F_0 generation Osborne-Mendel rats (10/sex/group) received 500, 1500, 3000, or 5000 ppm Methyl Salicylate in feed for 100 days, after which the animals were mated. There was no evidence of gross abnormalities. Various reproductive effects were observed, especially in the 2nd generation. In a continuous breeding reproductive toxicity study, male and female CD-1 mice (number not stated) were dosed orally with 25, 50, or 100 mg/kg Methyl Salicylate. Reproductive and fertility parameters were generally not affected. There also was no significant effect on mating behavior, fertility rate, or reproductive performance. Groups of CD-1 mice (20/sex/group) were dosed orally with 100, 250, or 500 mg/kg Methyl Salicylate in another continuous breeding reproductive toxicity study. A significant decrease in the mean number of litters, average number of pups/litter, proportion of live pups, and mean live pup weights was observed in the high dose group. CD rats (number not stated) received an oral dose of Methyl Salicylate (0.05 mL or 0.1 mL) on gestation day 10. The 0.1 mL dose group had decreased body weight gain, fewer and smaller neonates, and more resorptions and malformed neonates. Fetal kidney weight was decreased on gestation day 21, but was not different from the control on postnatal day 6.

Salicylic Acid

Groups of 20 gravid Wistar rats were fed a diet containing 0.06%, 0.1%, 0.2%, or 0.4% Salicylic Acid on gestation days 8 to 14.[1] Significant reproductive effects were observed in the 0.4% dietary group, and skeletal anomalies were observed in the 0.2% group. Only one dam gave birth to live neonates in the 0.4% dietary group, and skeletal anomalies were observed in 0.2% neonates. Groups of Wistar rats were dosed orally with Salicylic Acid at a dose of 75, 150, or 300 mg/kg on gestation days 8-14. Fetal mortality was 26% and 100% in the 150- and 300-mg/kg groups. Significant reproductive effects were observed in fetuses and neonates of the 150 mg/kg group. Groups of 10 Sprague-Dawley rats were dosed twice daily with 10 mg/kg Salicylic Acid on gestation days 20 and 21, and the mean gestation period was increased.

Sodium Salicylate

New Zealand White rabbits (number not stated) were dosed orally with 100 mg/kg Sodium Salicylate on gestation days 4 to 7.[1] The preimplantation ratio and average litter size were not affected, and teratogenic effects were not induced.

Two groups of 21 albino rats each received 200 mg/kg Sodium Salicylate orally on gestation days 6 to 15. A significant increase in resorptions and decrease in viable fetuses was observed in one group. A significant increase in external and internal abnormalities was observed in the second group, and skeletal anomalies were observed in both groups. Groups of 17 to 19 Sprague-Dawley rats received an oral dose of 30, 90, or 180 mg/kg Sodium Salicylate on gestation days 6 to 15. The incidence of teratogenicity was 30% in the 180 mg/kg group; marked embryotoxicity was observed and maternal toxicity was low. Regarding the 90- and 180-mg/kg groups, a dose-dependent decrease in growth was reported. Sprague-Dawley rats (number not stated) received oral doses of 1500 mg/kg and 300 mg/kg Sodium Salicylate, respectively, on gestation days 7, 8, 9, 10, or 11. Skeletal anomalies increased with dosing on days 8 and 10. Two groups of 2 CFE rats were dosed orally with 500 mg/kg Sodium Salicylate (on gestation day 8) or 100 mg/kg Sodium Salicylate (on gestation days 7 to 11). Results for the higher dose group included 50% maternal toxicity, 53% resorptions and dead fetuses, and 13% malformations. In the 100 mg/kg group, there was a 15% incidence of resorptions and dead fetuses. Groups of 12 to 15 albino rats received an oral dose of 25, 75, or 150 mg/kg Sodium Salicylate on gestation days 15 to 20. Parturition was delayed in one and two dams of the 25 and 150 mg/kg groups. In the 150 mg/kg group, neonatal mortality increased in a dose-dependent manner. In another experiment, in the same study, groups of 12 to 15 albino rats received an oral dose of 4.2, 12.5, or 25 mg/kg Sodium Salicylate on gestation days 20 to 21. In the 12.5 and 25 mg/kg groups, neonatal mortality increased in a dose-dependent manner. Groups of 10 Sprague-Dawley rats received an oral dose of 10 mg/kg Sodium Salicylate twice daily on gestation days 20 and 21. The duration of bleeding at parturition was increased. Thirteen of 121 neonates were born dead. Sprague-Dawley and Long-Evans rats (number not stated) received an oral dose of 125 or 175 mg/kg Sodium Salicylate on gestation days 8 to 10. No malformations were observed.

CD-1 mice (number not stated) received oral doses of 1500 mg/kg and 300 mg/kg Sodium Salicylate, respectively, on gestation days 7, 8, 9, 10, or 11. Fetal mortality increased with dosing on day 10. Skeletal anomalies increased with dosing on days 8 and 9. Groups of 19 or 37 CD-1 mice received doses of 2000 and 2600 mg/kg Sodium Salicylate on gestation day 8. Results for the 2000 mg/kg group were: 11% maternal mortality, 71% viable litters, 14% fetal mortality, and 7% of fetuses with malformations. Results for the 2600 mg/kg group were: 24% maternal mortality, 79% viable litters, 7% fetal mortality, and 3% of fetuses with malformations. Twenty-two CD-1 mice received an oral dose of 800 mg/kg

Sodium Salicylate on gestation days 8 to12. The average neonatal weight was decreased on postnatal days 1 and 3. Thirty ICR/SIM mice received an oral dose of 1600 mg/kg on gestation days 8 to 12, and 7 dams died. Neonate survival and the average number of viable neonates per litter on days 1 and 3 were significantly decreased and the number of dead neonates per litter on day 1 was significantly increased. Twenty-five A/Jax mice received an oral dose of 66.6 mg/mL Sodium Salicylate on gestation day 17. One dam delivered between 5 - 24 h. Fetal mortality was 47%, and the incidence of superficial, hepatic, and gastric hemorrhage was 6%, 1%, and 2% in dams killed at 24 h.[1]

Groups of 15 mated Crl:CD (SD)BR rats were given a single dose of 0 or 300 mg/kg (dose volume = 10 mL/kg) Sodium Salicylate (99.5% pure, in distilled water) on gestation day (GD) 9.[52] All fetal data, including all supernumerary ribs data, are presented as the percentage mean per litter. No statistical analysis was carried out on mean incidences of supernumerary ribs and the number of presacral vertebrae. In the treated group, adverse effects were noted on body weight changes and food consumption during the 2 days following dosing. At birth, a high majority of pups had extra ribs at the 300 mg/kg dose. Specifically, on postnatal day 1, 89% of pups from dams exposed to 300 mg/kg Sodium Salicylate had supernumerary ribs. For these pups, evidence of postnatal reversibility was observed in 10 out of 14 pups with rudimentary ribs and 26 presacral vertebrae. Radiographs done on postnatal days 1, 6, 14, 28, and 54 showed a reduction in the incidence of rudimentary ribs only, whereas extra ribs, often associated with 27 presacral vertebrae, had the same incidence from birth to adult stage. Furthermore, extra ribs seemed to exhibit similar growth evolution to the other thoracic ribs. The authors noted that dosing with Sodium Salicylate resulted in a significant increase in the incidence of supernumerary ribs. The length of gestation was not affected by treatment. At birth, the number of dead pups was slightly higher in the treated group (7 dead pups out of 15 litters) in comparison with the control group (3 out of 14 litters) but no external malformations were significantly increased in the treated group.

In a study involving mated female Sprague-Dawley rats, Sodium Salicylate was administered by gavage on GD 9 at a dose of 300 mg/kg (in distilled water).[53] Control animals received distilled water only. The females were killed on GD 13. The mean number of live embryos was slightly lower than the control group value (11.9 as compared to 14.7), mainly due to a slight, but non-significant, increased number of early resorptions in the treated group. Because Sodium Salicylate is known to cause an increased incidence of supernumerary ribs (see preceding study), the molecular basis of this defect was evaluated in this study by analyzing the possible involvement of *Hox* genes, known to specify vertebrae identity. On GD 13, the expression of several *Hox* genes, selected according to the position of their anterior limit of expression, namely upstream (*Hoxa9*), at the level (*Hoxa10*) and downstream (*Hoxd9*) to the morphological alteration, were analyzed. Posterior shifts in the anterior limit of expression of *Hoxa10* and *Hoxd9* were observed following exposure to Sodium Salicylate, which could explain an effect at the level of the axial skeleton. This finding suggests that the appearance of ectopic ribs can be attributed to an anterior transformation of lumbar vertebrae identity into thoracic vertebrae identity. The authors noted that whether this transformation occurs with all compounds inducing supernumerary ribs in rats remains to be determined.

Sodium Salicylate served as the positive control in an embryo-fetal developmental toxicity study.[54] The positive control (in distilled water) was administered intragastrically (dose = 250 mg/kg/day; once daily) to a group of 22 to 24 gravid female Sprague-Dawley rats on GDs 8 to 10. Sodium Salicylate was administered at a dose volume of 10 mL/kg/day. There were 4.8% malformations in fetuses from the positive control group, including exencephaly, cranial meningocele, spina bifida, gastroschisis, and subcutaneous ecchymosis. The rate of abnormality was significantly higher than that of the vehicle control group (p < 0.01). Additionally, there were significant decreases in the body and tail length, and mean body weight of fetuses in the positive control group when compared with the vehicle control group (p < 0.01).

Human

Dermal

Salicylic Acid

In the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings that may enhance systemic absorption.[55,56] Study details relating to dermal Salicylic Acid application and closure of the ductus arteriosus and oligohydramnios were not included.

<center>**Risk Assessment**</center>

Dermal

Salicylic Acid

The relative bioavailability of Salicylic Acid following facial application of a 30% Salicylic Acid peeling product (rinse-off product) was quantified by using plasma exposure parameters such as area under the plasma concentration-time curve (AUC) or C_{max} values.[57] The measured plasma Salicylic Acid levels were then compared to a single oral dose of 650 mg aspirin (acetylsalicylic acid). Upon absorption, aspirin is rapidly converted to Salicylic Acid, which circulates in the blood as salicylate.[58] Serum levels of salicylate typically reach a maximum 2 h after ingestion of aspirin. Blood concentrations of salicylate in excess of 300 µg/mL are considered toxic, while the effective concentration range for a therapeutic dose of aspirin is 150-300 µg/mL.[59]

The skin peel formulation containing 30% Salicylic Acid (equal to 7.7 mg/kg bw Salicylic Acid for a 60 kg person) was topically applied for 5 min in nine healthy male and female subjects. The mean (SD) Salicylic Acid C_{max} was 0.81 (0.32) µg/mL at 1.4 - 3.5 h after topical skin peel application, and was 56.4 (14.2) µg/mL at 0.5 - 1.5 h after oral aspirin administration.[57] The total area under the Salicylic Acid concentration versus time curve ($AUC_{0-\infty}$) was 6.4 µg × h/mL after dermal exposure and 320 µg × h/mL after oral exposure. The resulting AUC-based safety margin ratio was 50:1.

In comparison, the estimated Salicylic Acid C_{max} and AUC values at the maximum recommended oral aspirin dose (4000 mg, equivalent to 51 mg/kg bw Salicylic Acid for a 60 kg person) are 183 µg/mL and 1008 µg × h/mL, respectively. When compared to the C_{max} and AUC values at 30% Salicylic Acid rinse-off dermal dose, safety margin ratios of 229:1 and 158:1 for C_{max} and AUC, respectively, have resulted.[60] These results suggest a wide margin of safety with 30% Salicylic Acid use in rinse-off peeling products; when using human plasma exposure data, a margin of safety (MOS) of 10 is considered sufficient to ensure the safety of human exposure.[60,61]

The mean Salicylic Acid C_{max} of 0.81 µg/mL at 1.4 - 3.5 h after topical application of the peel product was compared to the blood concentrations of salicylate that are considered toxic (> 300 µg/mL)[58] as well as the blood concentrations of Salicylic Acid that are associated with salicylism (> 35 mg/dL [= 350 µg/mL]).[62] The results of these comparisons indicate that the blood concentration of Salicylic Acid resulting from application of the peel product (0.81 µg/mL) is substantially lower when compared to an approximation of the lowest blood concentration that is considered toxic (MOS = 300 µg/mL ÷ 0.81 µg/mL = 370), or an approximation of the lowest blood concentration that is associated with salicylism (MOS = 350 µg/mL ÷ 0.81 µg/mL = 432).

In order to determine the systemic burden after topical use of a skin care leave-on formulation (face and general creams) containing Salicylic Acid, another risk assessment was performed, taking into consideration the accumulative dose exposure to three leave-on skin care product types: body lotion, face cream, and hand cream. According to the Council's survey, Salicylic Acid is currently used in face and neck leave-on products at concentrations up to 2%, and in body and hand leave-on products at concentrations up to 0.2%.[18] For the purpose of this risk assessment, the estimated daily human exposure level to body lotion, face cream, and hand cream are 7.82, 1.54, and 2.16 g/day, respectively.[63]

In a risk assessment conducted by SCCNFP, a NOAEL of 75 mg/kg/day, derived from several rat oral teratogenicity studies on Sodium Salicylate, Acetyl Salicylate, Methyl Salicylate or Salicylic Acid, was used in the MOS calculation.[5] According to the test procedures, acetylsalicylic acid or Salicylic Acid was administered orally at various times during pregnancy (e.g., days 8 to 14 of gestation, days 9 and 11 of gestation, or days 7 to 17 of gestation) at daily doses of 75 to 500 mg/kg in rats. The results indicated that Salicylic Acid was neither teratogenic nor embryotoxic up to 75 mg/kg/day, and this NOAEL was derived from a series of animal studies in which Sodium Salicylate, Acetyl Salicylate, Methyl Salicylate, or Salicylic Acid were orally administered in rats. Above such dose, fetal malformations (skeletal malformations, cleft lip), resorptions and perinatal death were observed. Furthermore, in consideration of all available in vitro and in vivo data regarding human percutaneous absorption from topically applied Salicylic Acid, a dermal absorption value of 50% is chosen,[60] which also corresponds to the default absorption value proposed by SCCS.[63]

For leave-on skin care products, the relevant calculations are:

<center>Systemic exposure dose (SED) of body lotion =
7.82 g/day of product × 0.2 % maximum use concentration ÷ 60 kg person ×
50% skin absorption × 1000 mg/g conversion factor
= 0.130 mg/kg/day</center>

<center>SED of face cream =
1.54 g/day of product × 2 % maximum use concentration ÷ 60 kg person ×
50% skin absorption × 1000 mg/g conversion factor
= 0.257 mg/kg/day</center>

$$\text{SED of hand cream} =$$
$$\text{2.16 g/day of product} \times 0.2 \% \text{ maximum use concentration} \div 60 \text{ kg person} \times$$
$$50\% \text{ skin absorption} \times 1000 \text{ mg/g conversion factor}$$
$$= 0.036 \text{ mg/kg/day}$$

$$\text{Overall SED (leave-on skin care products, body lotion + face cream + hand cream)} =$$
$$0.130 + 0.257 + 0.036$$
$$= 0.423 \text{ mg/kg/day}$$

$$\text{MOS (leave-on skin care products)} =$$
$$\text{NOAEL (rat oral teratogenicity study) / Overall SED (sum of the three leave-on skin care products SEDs)}$$
$$= 75 \text{ mg/kg/day} / 0.423 \text{ mg/kg/day}$$
$$= 177$$

Plasma C_{max} and AUC values are available from kinetic studies involving applications of 2% Salicylic Acid leave-on formulations (either in cream or hydroalcoholic liquid) for 14 days, which resulted in a topical daily exposure to 0.45 mg/kg bw Salicylic Acid.[64] The AUC values for the cream and hydro-alcoholic formulations were about 366- to 252-fold lower than the AUC value from daily recommended oral therapeutic dose of aspirin (4000 mg, equivalent to 51 mg/kg bw Salicylic Acid).[60,64] In a kinetic-based safety assessment, total aggregate systemic exposure to Salicylic Acid from cosmetic products was calculated as 1.25 mg/kg bw/day, which yielded the C_{max} and AUC values of Salicylic Acid in human plasma at 7.0 µg/mL and 22 µg × h/mL, respectively. When compared to the estimated Salicylic Acid C_{max} and AUC values at the maximum recommended oral aspirin dose (183 µg/mL and 1008 µg × h/mL, respectively), the safety margins of 25- and 44-fold have resulted.[60]

Butyloctyl Salicylate

The following risk assessment was performed, taking into consideration that the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products of all types, and because of systemic toxicity concerns due to the potential for metabolism to salicylic acid.[27]

The Council survey of maximum reported use concentrations conducted in 2018 indicates that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration.[18] In accordance with the SCCS Notes of Guidance, the estimated daily exposure level for lipstick is 0.057g.[63] Thus, a total dose of Butyloctyl Salicylate exposure during the application of lipstick can be estimated:

$$\text{SED of lipstick} = 0.057 \text{ g/day of product} \times 35.9\% \text{ maximum use concentration} \div 60 \text{ kg person} \times 100\% \text{ skin absorption} \times 1000 \text{ mg/g conversion factor} = 0.34105 \text{ mg/kg/day}$$

$$\text{MOS (Butyloctyl Salicylate, lipstick)} = \text{NOAEL (from rat oral teratogenicity studies; see above) / SED}$$
$$= 75 \text{ mg/kg/day} / 0.1705 \text{ mg/kg/day}$$
$$= 220$$

Oral

Salicylic Acid

An exposure assessment of a representative cosmetic product (containing ≤ 2% Salicylic Acid) used on a daily basis estimated that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. This exposure assessment further contends that the reproductive and developmental toxicity from the daily use of a baby aspirin is not significant.[1]

GENOTOXICITY STUDIES

Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate,
Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate

Studies on the genotoxic potential of Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate are negative, except that Salicylic Acid is positive in a B. subtilis rec assay (negative in seven other bacterial tests and one mammalian test). Methyl Salicylate is positive in Salmonella typhimurium strains TA98, and TA100 with metabolic activation (negative in in 2 other Ames tests). Sodium Salicylate is positive in an in vivo chromosome aberration study in mice; it is negative for sister chromatid exchanges in vivo in mice, and in 4 in vitro test systems.[1]

Salicylic Acid

The mouse lymphoma assay (L5178Y mouse lymphoma cells) was used to evaluate the genotoxicity of Salicylic Acid (in deionized water) with and without metabolic activation.[46] Doses up to 1400 µg/mL were tested. Cyclophosphamide and methylmethanesulfonate served as positive controls. Salicylic acid was not genotoxic, with or without metabolic activation, at any of the doses tested.

Sodium Salicylate

The genotoxicity of Sodium Salicylate was evaluated in a mammalian cell genotoxicity test involving Chinese hamster ovary (CHO) cells.[43] The test substance was evaluated at concentrations up to 0.5 mM with and without metabolic activation. Sodium Salicylate was not genotoxic over the range of concentrations tested (0.06 to 0.5 mM), both with and without metabolic activation. The positive control (*N*-ethyl-*N*-nitrosourea) was genotoxic.

CARCINOGENICITY STUDIES

Salicylic Acid has been classified as a non-carcinogen; however, relevant details that would have served as a basis for this classification were not provided .[1]

In Vitro

Salicylic Acid and Sodium Salicylate

Sodium Salicylate had dose-dependent inhibitory effects on adenoma, in vitro transformants of adenoma, and carcinoma cell lines. IC_{50} values of 1.65 to 7.28 mM were reported.

Animal

Dermal

Methyl Salicylate

A skin painting study was performed in which Methyl Salicylate was applied to the back of 39 mice, at biweekly intervals, for 400 days.[1] Neoplasms were not induced.

Parenteral

Groups of 15 male and 15 female A/He mice were dosed intraperitoneally with 100 or 500 mg/kg Methyl Salicylate in tricaprylin 3 times per week for 8 weeks (24 doses total).[1] Two out of 13 males and 1 of 14 females of the low-dose group that survived until study termination had lung tumors. One out of 12 males and 5 of 13 females of the high-dose group that survived until study termination had pulmonary tumors. These compare with 10 of 46 males and 8 of 48 females with tumors in the untreated control group and 8 of 30 males and 10 of 28 females with tumors in the vehicle control group.

Photocarcinogenicity

Salicylic Acid

In a National Toxicology Program (NTP) photocarcinogenicity study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing Salicylic Acid were evaluated.[65] Creams containing Salicylic Acid (0%, 2%, or 4%), were applied to the skin of groups of 18 male and 18 female hairless mice in the mornings. Additional

groups of 36 male and 36 female mice were not exposed to the cream. In the afternoons, groups of animals were exposed to one of three strengths of synthetic solar light for 4 h. Other groups were not exposed to light and were control groups. The treatment and exposures were performed five days per week for 40 weeks, during which time the animals were monitored for the development of skin cancers. Greater strengths of light increased the incidences of skin cancers in mice not given a cream or given a cream with no acid included. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities. It was concluded that Salicylic Acid had some protective effect against photocarcinogenicity at lower intensities.

Tumor Promotion

Salicylic Acid inhibited tumor promoter 12-O-tetradecanoylphorbol-13-acetate-induced transformation in a concentration-dependent (concentrations not stated) manner, in a culture model (mouse epidermal JB6 cells)that was used to study tumor promotion and anti-tumor promotion.[1]

OTHER RELEVANT STUDIES

Estrogenic Activity

Butyloctyl Salicylate and Ethylhexyl Salicylate

The estrogenic activity of Butyloctyl Salicylate and Ethylhexyl Salicylate was studied.[66] A consensus modeling method to predict their qualitative and quantitative binding activity towards the estrogen receptor (ER) was used. The consensus modeling comprised two Decision Forest (DF) models that were built using two different training data sets. The two DF models were validated using 5-fold cross validations and external chemicals. Similar predictions were made on unrelated compounds. Prediction confidence was defined as a number between 0 and 1, for indication of confidence for a prediction; the smaller the number, the less confident the binding affinity prediction. The experimental ER binding affinities were given as logarithmic relative binding affinity (log10RBA) values to the hormone estradiol. RBA is defined as the relative binding affinity to the natural estrogen, estradiol. The RBA of estradiol is set at 100; thus, its log10RBA = 2. Ethylhexyl Salicylate was classified as an estrogen receptor non-binder. Butyloctyl Salicylate was classified as having binding activity to the ER (prediction confidence value = 0.827; log10RBA = -0.853).

A recombinant yeast estrogen assay was used to assess the activity of Ethylhexyl Salicylate.[67] The ERα gene, together with expression plasmids (containing estrogen responsive elements and the lac-Z reporter gene encoding the enzyme β-galactosidase), were incubated in medium containing Ethylhexyl Salicylate (10 μl, serially diluted in ethanol) and the chromogenic substrate, chlorophenol red-β-D-galactopyranoside (CPRG). Active ligands (which bind to the receptor) induce β-galactosidase (β-gal). The relative potency of the test substance was determined only when the dose–response curve was parallel to that of 17-β-estradiol. To do so, the concentration of the test substance required to produce a half-maximal response (absorbance at 540 nm (A540) between 1.7 and 2.0) was divided by the concentration of 17-β-estradiol required to produce the same response. Compounds displaying a submaximal response were compared at the 10% response level. Ethylhexyl Salicylate generated a dose-response curve that was shallower than the one for 17-β-estradiol, and had a submaximal response for estrogenic activity (estrogenic potency relative to 17-β-estradiol = 1/2,000,000).

Effect on Cytokine Production

Methyl Salicylate

Respiratory and skin local lymph node assays (LLNAs) were used to evaluate the effects of inhalation exposure to respiratory and contact sensitizers on cytokine profiles. Methyl Salicylate (a respiratory and skin irritant) served as the negative control in both assays. Six male BALB/c mice were exposed (head/nose-only) to Methyl Salicylate (30 mg/m^3) in a short-term exposure respiratory LLNA.[68] The animals were exposed for 45, 90, 180, or 360 min/day on 3 consecutive days (days 0, 1, and 2). For inhalation exposure, the chemical was evaporated in air without solvent. A control group of 6 mice exposed to air only for 360 min/day. Three days after the last inhalation exposure, the draining lymph nodes were excised and cytokine production was measured after ex vivo stimulation with Concanavalin A. Cytokine profiles were assessed. Skin application was used as a positive control in this study. In the skin LLNA, the dermal route (single ear application; n = 3 male BALB/c mice) was used as a positive control. The negative control Methyl Salicylate (25%, 25 μl), dissolved in acetone:olive oil (4:1) solution (AOO), was applied on the dorsum of both ears (50 μl per animal) for 3 consecutive days (days 0, 1, and 2). A vehicle (AOO) control group of 6 mice was also included. On day 5, auricular lymph nodes were collected and used for ex vivo cell proliferation and cytokine measurements. After inhalation exposure and skin exposure, Methyl Salicylate did not induce a measurable interleukin-4 (IL-4) response (i.e., no significant cytokine production).

<center>**DERMAL IRRITATION AND SENSITIZATION STUDIES**</center>

The skin irritation and sensitization studies summarized below (except for italicized text) are presented in detail in Table 4. In addition to these studies, it should be noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus (specific studies not included).[69]

<center>**Irritation**</center>

Animal

Dermal

The application of 500 mg (in 0.5 mL) of Isodecyl Salicylate (6 male New Zealand white rabbits) and Tridecyl Salicylate (6 female Dunkin-Hartley albino guinea pigs), and Butyloctyl Salicylate (rabbits, dose administered not stated) did not cause skin irritation.[1] Undiluted Ethylhexyl Salicylate produced mild skin irritation in rabbits (number not stated). Methyl Salicylate (concentration not stated) has been reported to cause severe skin irritation in guinea pigs (number not stated) and moderate skin irritation (abraded and intact skin) in rabbits (number not stated). Repeated applications of Methyl Salicylate (concentration not stated) to guinea pigs (number not stated) caused scaling, dryness, and isolated and multiple infiltrates by days 4 to 6. Threshold changes were noted with the application of a 50% oil solution. At concentrations of 1%, 3%, and 6% (in 70% ethanol), Methyl Salicylate was severely irritating to the skin of all 3 animals (species not stated) tested. However, this was not true for water suspensions of the 3 Methyl Salicylate concentrations.

The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 Albino angora rabbits and 6 male Hartley guinea pigs.[70] After 24 h, Amyl Salicylate was severely irritating to the skin of rabbits and mildly irritating to the skin of guinea pigs. The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 miniature swine of the Pitman-Moore Improved strain. Skin irritation was not observed following a 48-h application. When undiluted Ethylhexyl Salicylate was applied under occlusion to the skin of 4 rabbits for 24 h, mild erythema was observed.[7] These results are reported in the acute dermal toxicity study that is summarized earlier in this report. In another test, the application of undiluted Ethylhexyl Salicylate to the skin of 3 rabbits did not result in skin irritation.[30]

Groups of 5 male hrBR outbred hairless albino guinea pigs received a single ~ 2 h application of Hexyl Salicylate at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or at 100%. Skin irritation was not observed. In a test involving 4 male albino Dunkin/Hartley strain guinea pigs, the animals were treated topically with patches saturated with 10%, 25%, or 50% Hexyl Salicylate in acetone.[8] After 24 h, no irritation was observed at the 10% concentration, and very slight erythema was observed in 3 animals at the 2 highest concentrations. In another test (same protocol), the skin irritation potential of Hexyl Salicylate (0.1 to 2% in 0.01% dodecylbenzenesulfonate/saline) was evaluated using 4 male albino Dunkin Hartley guinea pigs.[8] Very slight erythema was observed at a concentration of 0.1% and slight erythema and edema were observed at higher concentrations. The application of undiluted Hexyl Salicylate (20 µl/5 cm^2) to the skin of 2 miniature swine did not cause skin irritation.[8] In a study involving 3 or 4 female New Zealand white rabbits, Hexyl Salicylate was applied for 4 h to the skin at concentrations ranging from 10% to 100%. Skin irritation was not observed at concentrations of 10% and 25%, but irritation was observed at higher concentrations.[8] When undiluted Hexyl Salicylate was applied (5 g/kg) to the skin of 10 rabbits, skin irritation was observed in 8 animals.[8] Also, when undiluted Hexyl Salicylate (20 µl/5 cm^2) was applied to the skin of 6 hairless mice, skin irritation was not observed.[8]

In a study in which Methyl Salicylate was applied to the skin of 6 rabbits at concentrations up to 100%, skin irritation was observed only at concentrations of 25% and 100%.[46] The skin irritation potential of wintergreen oil (containing 80 - 99% Methyl Salicylate) was evaluated using 6 hairless mice and 2 miniature swine.[9] Flaking, hyperkeratosis and dry desquamation were observed. The application of Methyl Salicylate (3%) to the skin of 6 to 8 male and female outbred, Himalayan white-spotted guinea pigs for 21 days resulted in minimal skin irritation.[71] Also, when Methyl Salicylate (3%) was applied for 24 h to guinea pigs (6 to 8) of the same strain, mild erythema was observed in at least 25% of the animals.[71] A single dermal dose (5 g/kg) of undiluted Methyl Salicylate caused slight erythema and edema in 2 of 9 rabbits and moderate erythema and edema in 7 of 9 rabbits (skin irritation results from acute dermal toxicity study).[9] In a mouse ear swelling test, the minimal irritating concentration of Methyl Salicylate was determined to be 20%.[72] When Salicylic Acid (0.5 g in water) was applied to the skin of 3 rabbits, there was no evidence of skin irritation.[4,73] However, when alcoholic solutions containing 2% Salicylic Acid were applied to the skin of rabbits, mild to no skin irritation was reported.[4] Formulations containing 3.5%, 5.0%, and 7.5% Salicylic Acid caused significant macroscopic alterations (desquamation, inflammatory reaction and comedogenic effect), compared to the negative control, when applied daily to the ears of 6 male albino New Zealand rabbits.[74] Salicylic Acid concentrations of 10% and 25%, but not 2% (in propylene glycol ether in ethanol), applied repeatedly caused skin irritation in rabbits.[5] Cleansing formulations (containing 0.5% Salicylic Acid or diluted with water to contain 0.25% Salicylic Acid) caused transient irritation when applied repeatedly to the skin of rabbits.[5] Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle) caused slight

to marked erythema when applied repeatedly to the skin of rabbits.[5] Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs resulted in mild skin irritation.[4] Sodium Salicylate (0.5 g in water) was non-irritating to the skin of 3 rabbits.[43]

Intradermal Injection

After 0.1% Hexyl Salicylate (0.1 mL) was injected intradermally into the skin of 4 inbred Hartley strain albino guinea pigs, skin irritation was observed.[75] The intradermal injection of a higher concentration of Hexyl Salicylate (5%) into the skin of 4 guinea pigs (same strain) did not cause skin irritation. The vehicle was not reported in either experiment, and an explanation for the different results was not provided.

Human

Dermal

Clinical tests for cumulative irritation are available for the following ingredients at the specified concentrations: Salicylic Acid (27 subjects; 2% - minimal cumulative irritation; 1.5% - slight or no irritation); TEA-Salicylate (10% caused irritation in 1 of 12 subjects); Methyl Salicylate (12% to 50% - pain and erythema (5 subjects); 8% - no irritation (number of subjects not stated); 1% aerosol – erythema (4 subjects); Ethylhexyl Salicylate (4% - no irritation (number of subjects not stated)); and Tridecyl Salicylate (no irritation, 30 subjects).[1]

In a 48-h occlusive patch test, Amyl Salicylate (32% in acetone) was not irritating to the skin of 50 subjects.[70] In a 48-h closed patch test involving 23 male subjects, 4% Ethylhexyl Salicylate in petrolatum did not cause skin irritation.[7] Skin irritation was observed when undiluted Hexyl Salicylate was evaluated in a 4-h patch test using 30 volunteers.[76] In a 24-h patch test involving 56 subjects, Hexyl Salicylate was evaluated for skin irritation potential at concentrations of 0.3%, 3%, or 30% in 3:1diethyl phthalate:ethanol.[8] Results were negative. Skin irritation was not observed after 8% Methyl Salicylate (in petrolatum) was applied to the backs of 27 male subjects.[9] The same results were reported when or 12% wintergreen oil (containing 80 – 99% Methyl Salicylate) in petrolatum was applied to the backs of 25 subjects. Repeated applications of 30% and 60% Methyl Salicylate to the skin of 9 subjects resulted in skin irritation.[77] A cream containing 2% Salicylic Acid was classified as non-irritating after repeated patch applications to the skin of human subjects (number not stated).[5] Surfactant-based products containing 2% Salicylic Acid (pH 3.8; diluted test concentration not stated) were mildly irritating when applied repeatedly to the skin of human subjects (number not stated).[5] Repeated applications of a cream containing 1.5% Salicylic Acid to the skin of human subjects (number not stated) caused slight skin irritation.[5] A hydroalcoholic gel containing 2% Salicylic Acid was slightly irritating when applied repeatedly to the skin of human subjects (number not stated).[5] Different results were reported for two creams (1 non-irritating; the other moderately irritating) containing 2% Salicylic Acid that were applied repeatedly to the skin of human subjects (number not stated).[5] In a repeated open application test, a cream containing 2% Salicylic Acid that was applied to the backs of human subjects (number not stated) did not cause reactions that were different from those induced by the control.[5]

When a shampoo containing 3% Salicylic Acid was applied (as a 4% dilution) continuously under a patch to the skin of human subjects, a potential for skin irritation was demonstrated.[5] In exaggerated use repeated application tests in which results for shampoos containing Salicylic Acid at concentrations of 2% and 3% were compared with a placebo, there were no statistically significant differences in combined irritation or transepidermal water loss (TEWL).[5] It was noted that, at a concentration of 3% Salicylic Acid in rinse-off shampoo formulations, this concentration does not appear to be more irritating than other components of the formulations. Daily application (2 weeks) of a hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82) to the skin of human subjects did not cause skin irritation.[5] In 2 home use tests (6 weeks) involving products containing 2% Salicylic Acid, mild skin irritation was observed.[5] In another home use test (14 weeks), involving products containing 2% Salicylic Acid, mild skin reactions were observed in 12 of 194 subjects.[5]

Sensitization

In Vitro/In Chemico

In a genomic allergen rapid detection assay utilizing an in vitro model of dendritic cells, Hexyl Salicylate was predicted to be a skin sensitizer.[78] An integrated testing strategy for skin sensitization that focuses on 3 methods (human cell line activation test (h-CLAT) [assesses surface markers on dendritic cell lines], direct peptide reactivity assay (DPRA) [measures reactivity with model proteins], and the Sens-IS assay [measures the gene expression of irritation and sensitization biomarkers]) covering the first three steps of the adverse outcome pathway was used to determine the skin sensitization potential of Salicylic Acid.[79] The results were equivocal, but, ultimately, were considered positive. The allergen–peptide/protein interaction assay was also used to predict the sensitization potential of Salicylic Acid.[80] Mass spectra of both

target peptides revealed neither any modification of peptide-21 nor of peptide-20 by Salicylic Acid, under various pH conditions.

Animal

Maximization test data on Butyloctyl Salicylate indicate that none of the guinea pigs induced with 5% Butyloctyl Salicylate (intradermally) and 100% Butyloctyl Salicylate (topically) and challenged with 100% Butyloctyl Salicylate had a sensitization response.[1] However, one of the 10 guinea pigs challenged with 50% Butyloctyl Salicylate had a clear dermal response. Maximization test data on Ethylhexyl Salicylate indicate that skin sensitization was not observed in guinea pigs(number not stated) induced with 2.5% Ethylhexyl Salicylate (intradermally) and 50% Ethylhexyl Salicylate (topically) and challenged with a 25% solution of Ethylhexyl Salicylate in ethanol/diethyl phthalate (DEP) (1:1).[1] Results for Methyl Salicylate are negative at concentrations up to 25%, independent of vehicle, in the local lymph node assay.[1] A modified Magnusson-Kligman guinea pig maximization test on Methyl Salicylate was performed using 10 Dunkin-Hartley guinea pigs. The animals were induced with 2.5% Methyl Salicylate (intradermally) and 100% Methyl Salicylate (topically) and challenged with 10% Methyl Salicylate in acetone, and results were negative. In another maximization test, albino Dunkin-Hartley guinea pigs (number not stated) were induced with 2.5% Methyl Salicylate (intradermally) and 100% Methyl Salicylate (topically) and challenged with 10% Methyl Salicylate in acetone/PEG 400 (70:30). Test results were negative for skin sensitization. Although results for Salicylic Acid are positive in the LLNA at a concentration of 20% in acetone, this is not true for Salicylic Acid at a concentration of 20% in acetone/olive oil.[1]

In the murine LLNA, a very low EC3 (0.18%; EC3 = effective concentration that induces a 3-fold increase in local lymph node proliferative activity) was reported for Hexyl Salicylate.[79] The lower the EC3 value, the greater the sensitization potency. It was noted that the low value reported may have been due to possibly sensitizing impurities. Hexyl Salicylate was tested in a sensitization study involving 10 inbred Hartley albino guinea pigs.[75] Sensitization was observed after the second challenge with 0.1% Hexyl Salicylate (intradermal injection) and 5% Hexyl Salicylate (topical application). In a sensitization test using groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs, challenge with 50% Hexyl Salicylate in 3:1 diethyl phthalate (DEP):ethanol and 100% Hexyl Salicylate did not induce sensitization.[8] A maximization test was performed to evaluate the sensitization potential of Hexyl Salicylate in a group of 10 albino Dunkin Hartley guinea pigs.[8] Sensitization was not observed after challenge with 10% Hexyl Salicylate. The sensitization potential of Methyl Salicylate (0.7 μM) was evaluated using the LLNA.[81] Overall, the results were classified as negative. According to another source, 50% Methyl Salicylate was predicted to be a non-sensitizer using the LLNA.[82] Salicylic Acid has been tested and found to be a non-sensitizer in the LLNA.[83] In a modified Buehler test, Methyl Salicylate (25% w/v in hydro-alcoholic solution) did not cause skin sensitization in a group of 20 guinea pigs.[4] The same was true for Salicylic Acid (25% w/v in hydro-alcoholic solution) when tested according to the same procedure.[4]

Human

In a maximization test involving 25 subjects challenged with 10% Salicylic Acid, results were negative.[1] Results were also negative for skin sensitization in a human repeated insult patch test (HRIPT; 99 subjects) on a moisturizer cream containing 2% Salicylic Acid and in an HRIPT (101 subjects) on both a moisturizing cream and a moisturizing lotion containing 2% Salicylic Acid. Gels containing 2% Salicylic Acid were also non-sensitizers in HRIPTs involving 193 subjects and 198 subjects. In a maximization test involving 23 subjects, 4% Ethylhexyl Salicylate in petrolatum did not induce skin sensitization. Also, in a maximization test involving 27 subjects, 8% Methyl Salicylate in petrolatum did not induce skin sensitization.

Neither skin irritation nor sensitization was observed in a human repeated insult patch test (HRIPT) in which 52 subjects were patch tested with undiluted Butyloctyl Salicylate.[47] Hexyl Salicylate has been classified as a Category 4 substance (infrequent cause of contact allergy in relation to level of exposure) with regard to its human skin sensitization potential.[83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 4 are rarely important clinical allergens, because they require considerable/prolonged exposure to higher dose levels to produce sensitization, which even then is unlikely to exceed 0.01% of those exposed. Furthermore, a human skin sensitization NOEL of 35,433 μg/cm^2 has been reported for Hexyl Salicylate. HRIPT results for 30% Hexyl Salicylate in 3:1DEP:ethanol were negative for skin irritation and sensitization.[8] In a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 μg/cm^2.[79] In another maximization test involving 22 subjects patch tested with 3% Hexyl Salicylate, the results were negative for skin irritation and sensitization.[8]

Methyl Salicylate has been classified as a Category 5 substance (a rare cause of contact allergy except perhaps in special circumstances, e.g., use in topical medicaments) with regard to its human skin sensitization potential. [83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. It was also noted that there are insufficient data (availability of specific data not mentioned) to define a human skin

sensitization NOEL. Category 5 consists of substances that have a very low intrinsic ability to cause skin sensitization. Here, typically only exceptionally prolonged exposure in combination with high use levels will lead to skin sensitization, for example, routine use in medicaments for treatment of chronic skin conditions. For these materials, sensitization in the general population is likely to be (extremely) rare. In a maximization test involving 25 subjects, 12% wintergreen oil (containing 80 – 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum did not induce skin sensitization.[9] In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate was a non-sensitizer.[9] Product formulations containing 2% Salicylic Acid did not cause sensitization in HRIPTs (test populations: 84 to 198 subjects).[5] Salicylic Acid has been classified as a Category 6 substance with regard to its human skin sensitization potential.[83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 6 are essentially free from skin sensitizing activity (i.e., non-sensitizers). Further details were not included.

Computational Analyses/Predictions

Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate

A database of 259 heterogeneous organic compounds (including Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate) evaluated in the guinea pig maximization test was subjected to multivariate quantitative structure-activity relationship (QSAR) analysis, utilizing principal component analysis and linear discriminant analysis.[84] Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate were classified as non-sensitizers. A QSAR system for estimating skin sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and/or their activated metabolites to react with skin proteins has also been developed.[85] Amyl Salicylate was one of the chemicals that was identified to fall within the model domain accounting for the first neighbors of centered atoms, and was predicted to be a non-sensitizer.

A study was performed to validate a QSAR rank model for grading allergenic potency using a database of 74 known allergens and non-allergens that were chosen among fragrance chemicals in common use.[86] The model's scoring system for class levels was: Class 1 (non-allergic; scores = 0.63 to 1.97), Class 2 (weak to mild; scores = 1.24 to 3.10), Class 3 (moderate; scores = 1.81 to 4.14), and Class 4 (strong to extreme; scores = 2.66 to 4.88). Hexyl Salicylate and Methyl Salicylate were classified as non-allergic.

Risk Assessment

Hexyl Salicylate

An exposure-based quantitative risk assessment (QRA) methodology was used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate, and an International Fragrance Association (IFRA) standard was issued.[87] The following relevant sensitization data were used for implementation of the QRA: LLNA weighted mean EC3 value (45 $\mu g/cm^2$), human data: NOEL – HRIPT (induction) (35,433 $\mu g/cm^2$), experimental NOEL – MAX (induction) (2069 $\mu g/cm^2$), and weight of evidence (WoE) no expected sensitization induction level (NESIL) (35,400 $\mu g/cm^2$).[8]

Photosensitization/Phototoxicity

The photosensitization/phototoxicity studies summarized below are presented in detail in Table 5.

In Vitro

Ethylhexyl Salicylate

The phototoxicity of Ethylhexyl Salicylate (0.1 to 316 $\mu g/mL$) was evaluated in the 3T3 neutral red uptake phototoxicity test, using a cell suspension of 3T3 fibroblasts.[88] Phototoxicity test results were classified as negative.

Animal

Hexyl Salicylate

Undiluted Hexyl Salicylate (20 μl) was not phototoxic in 6 Skh:hairless-1 mutant mice exposed to light from a long arc xenon lamp and fluorescent blacklight lamps .[8,89] Phototoxicity also was not observed in 2 miniature swine tested with undiluted Hexyl Salicylate (20 μl) according to the same procedure.[8,89] In a phototoxicity study in which two groups of 5 Crl:IAF(HA)-hrBR outbred, albino hairless guinea pigs were exposed to Hexyl Salicylate (concentrations up to 100%) and then ultraviolet radiation (UV) from a long-arc xenon water-cooled lamp, results were also negative.[8] Photoallergy was not

observed in 2 groups of 5 Crl:IAF (HA)-hrBR outbred albino hairless guinea pigs exposed to Hexyl Salicylate (50% and 100%) plus UV.[8]

Methyl Salicylate

Methyl Salicylate (50% in DEP) was evaluated for phototoxicity and photoallergenicity potential using 25 guinea pigs. Both evaluations involved exposure to long-wavelength ultraviolet radiation (UVA) and mid-wavelength ultraviolet radiation (UVB), and the test substance was classified as non-phototoxic and non-photoallergenic.[46] The phototoxicity of wintergreen oil (containing 80 – 99% Methyl Salicylate) in the presence of UVA was evaluated using 2 miniature swine. Results were negative.[9]

Salicylic Acid

The contact photosensitization potential of Salicylic Acid was determined using groups of 5 female albino outbred ICR mice.[1] The animals were challenged with 25% Salicylic Acid in alcohol (20 μl), followed by irradiation for 2.5 h, and results were negative.

Tridecyl Salicylate

Ten male Hartley albino guinea pigs were used to determine the phototoxicity potential of Tridecyl Salicylate.[1] During induction 2% Tridecyl Salicylate (0.5 mL) was applied to the back daily for 3 weeks, and the test site was irradiated with UVA + UVB. At challenge with 0.1% Tridecyl Salicylate in dehydrated alcohol, results were negative.

Human

Hexyl Salicylate

In a study involving 56 subjects patch tested with Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 DEP:ethanol), followed by irradiation of sites with UVA and UVB, no reactions were observed.[8]

Ethylhexyl Salicylate and Salicylic Acid

Products containing 2% Salicylic Acid did not induce phototoxicity in studies involving groups of 10 human subjects. The same was true for these products in photoallergenicity studies involving groups of 25 to 28 humans subjects.[1] A cream containing 2% Salicylic Acid had a photoprotective effect in a study involving 5 subjects. The same was true for a formulation containing Ethylhexyl Salicylate (concentration not stated) in groups of ≤ 38 subjects.

OCULAR IRRITATION STUDIES

In Vitro

Sodium Salicylate

Sodium Salicylate was evaluated using the EpiOcular™ reconstructed human cornea-like tissue model.[90] The tissues are cultured from primary non-transformed human epidermal keratinocytes (NHEK) obtained from individual donors. The tissues were incubated with Sodium Salicylate (50 μl) for 30 minutes, and tissue viability was assessed using the MTT assay. If the treated tissue viability was ≤ 60% relative to negative control tissue viability, the test chemical was predicted as "in vitro irritant." Values for percent viability were 5% (run #1) and 5.1% (run #2) for Sodium Salicylate, classifying the chemical as an ocular irritant.

Animal

The ocular irritation potential was negative for the following ingredients: Butyloctyl Salicylate (concentration not stated; 6 rabbits tested) Ethylhexyl Salicylate (50% solution; number of rabbits not stated), Isodecyl Salicylate (10% in liquid paraffin; 6 New Zealand albino rabbits tested), and Tridecyl Salicylate (0.1 mL dose; 3 male New Zealand white rabbits).[1] Methyl Salicylate was not irritating in one study using rabbits, but was severely irritating in another study to the eyes of guinea pigs (test concentrations and number of animals not stated in either study).

Ethylhexyl Salicylate

The ocular irritation potential of undiluted Ethylhexyl Salicylate was evaluated using 3 New Zealand White rabbits.[30] The test substance (0.1 mL) was instilled into 1 eye of each animal, and the eyes were not rinsed. Reactions were scored at ~1 h, 24 h, 48 h, and 72 h post-instillation. On day 1, a slight or moderate chemosis and a slight or moderate conjunctival redness were observed in all 3 animals. In 1 rabbit, slight chemosis remained on day 2. In 2 rabbits, slight redness was observed until day 3. Ocular reactions were not observed on day 4. The test substance was classified as non-irritating.

Methyl Salicylate

A rabbit eye irritation test was conducted in 5 healthy albino rabbits. A 0.005 mL aliquot of neat Methyl Salicylate was applied to the center of the cornea while the lids were retracted.[91] One minute later the lids were released. The eyes were examined 18 - 24 h later in strong diffuse daylight and then stained with fluorescein. Methyl Salicylate caused necrosis on 13 to 37% of the cornea (visible after staining).

A rabbit eye test was conducted in 3 healthy albino rabbits.[9] One-tenth mL of 1.25% Methyl Salicylate in specially denatured alcohol (SDA) 39C was instilled into the right eye of each rabbit with no further treatment. The untreated left eye served as control. Observations were made every 24 h for 4 days and then again on day 7 according to the Draize method. Intense conjunctival irritation accompanied by chemosis and considerable discharge was observed in all 3 rabbits. The treated eyes were normal on day 7 of observation.

Salicylic Acid

The Draize test was used to evaluate the ocular irritation potential of Salicylic Acid (purity not stated) in 3 rabbits (strain unknown).[73] The test substance (100 g) was instilled into the right eye of each animal, and the eyes were not rinsed. Instillation of the test substance was followed by a 21-day observation period. Salicylic Acid caused severe ocular irritation, and reactions did not clear during the 21-day observation period. Numerous formulations (non-alcoholic and hydroalcoholic) that contained Salicylic Acid at concentrations ranging from 0.05% to 2% have been evaluated in the Draize test (rabbits).[5] The study authors considered these formulations to be mild irritants when instilled into the eyes of rabbits.

Sodium Salicylate

The ocular irritation potential of Sodium Salicylate was evaluated using 3 female New Zealand White rabbits.[43] The test substance (0.1 g) was instilled into the left eye (followed by rising with saline), and reactions were scored at 1 h, 24 h, 48 h, 72 h, and day 7 post-instillation. None of the animals died, and there was no evidence of systemic toxicity. Ocular irritation was observed in all animals and reactions cleared within day 7. Sodium Salicylate was classified as mildly irritating to the eyes of rabbits.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Amyl Salicylate

A total of 1323 patients (from 11 centers combined) were patch tested with fragrances.[92] Patch testing was performed with Finn chambers on Scanpor tape; patches were applied to the back for 2 days. Readings were made according to International Contact Dermatitis Research Group (ICDRG) guidelines on days 2 and 3, or on days 2 and 4. Twenty-eight irritant or doubtful reactions (on day 3 or 4) to a total of 19 fragrance materials were reported. Two reactions (irritant or doubtful) were reported for 1% Amyl Salicylate.

A population of 1855 patients (6 European dermatology departments combined), was patch tested with fragrances.[93] Finn Chambers on Scanpor tape were used in all centers except 1(at which van der Bend chambers were used). Readings were taken at most centers on days 2 and 4. The reading at day 3 or day 4 was used for overall evaluation of positive test results. Three patients had a positive reaction (+) to 5% Amyl Salicylate, and 5 had doubtful reactions.

Hexyl Salicylate

In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested with various fragrance materials according to internationally accepted criteria.[94] No reactions were observed with 5% Hexyl Salicylate in petrolatum.

Case Reports

Methyl Salicylate

A man became acutely ill (within less than an hour) after using an herbal skin cream containing Methyl Salicylate (high concentration, value not stated) for the treatment of psoriasis.[95] The area of application was covered with an occlusive wrap. Signs of metabolic acidosis superimposed on respiratory alkalosis and a serum salicylate level of 48.5 mg/dL were reported. These signs declined after the patient received treatment for the metabolic acidosis and respiratory alkalosis. The author noted that the transcutaneous absorption (described as rapid) of Methyl Salicylate was enhanced due to the abnormal areas of skin and use of an occlusive dressing. It was concluded that acute salicylate toxicity may result from the topical administration of Methyl Salicylate.

Salicylic Acid

Although rare, toxicity can occur from topical application of Salicylic Acid (i.e., salicylism).[62] Salicylism can be acute or chronic and develops when blood concentrations of salicylate are greater than 35 mg/dL. Symptoms of salicylism include nausea, confusion, dizziness, delirium, psychosis, stupor, and coma.

Dermal Salicylic Acid hypersensitivity was observed in a case report on a woman with no medical history and no known allergies.[96] The patient had applied an OTC topical Salicylic Acid for the treatment of warts on both hands. The first application was without incident, but a second application the next day caused finger swelling within minutes and then pain and loss of finger mobility. The authors noted that this hypersensitivity reaction to topical Salicylic Acid application is rarely seen.

**Amyl Salicylate, Ethylhexyl Salicylate, Methyl Salicylate,
Salicylic Acid, and Sodium Salicylate**

A woman with a 12-year history of rosacea was advised to use a sunscreen that contained Ethylhexyl Salicylate during several months prior to intense pulsed-light treatment for facial telangiectasia.[97] One-half year later, the patient developed facial dermatitis. She had a positive (++) patch test reaction to 2% Ethylhexyl Salicylate in petrolatum, a positive (+) patch test reaction to 5% Ethylhexyl Salicylate in petrolatum, and a positive (++) patch reaction to the sunscreen product. Results of repeated open application tests (ROATs) with Ethylhexyl Salicylate, 2% and 5%, were positive from day 4 on. A total of 29 consecutive eczema patients acting as controls were negative to Ethylhexyl Salicylate (at 5% and 2% in petrolatum). The patient was retested after 1 year, and the (+) reaction to Ethylhexyl Salicylate was reproduced. Patch test results for the following other salicylates were negative: Amyl Salicylate (5% in petrolatum), Methyl Salicylate (2% in petrolatum), Salicylic Acid (2% in petrolatum), and Sodium Salicylate (2% in petrolatum).

A woman who used a sunscreen containing Ethylhexyl Salicylate and had a history of rhinitis and intrinsic bronchial asthma developed erythematous micropapules (that progressed to microvesicles and vesicles) on the back, chest, and abdomen.[98] A skin biopsy of the lesions revealed a dermal hypersensitivity reaction that was consistent with contact dermatitis. Epicutaneous tests of the components of the sunscreen spray product were performed. Results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for any of the other ingredients tested. Patch test results for the following other salicylates were negative: Methyl Salicylate, Sodium Salicylate, and Salicylic Acid. Photopatch test results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for Methyl Salicylate, Sodium Salicylate, or Salicylic Acid.

Methyl Salicylate, Salicylic Acid, and Salicylates

Numerous case studies report toxic reactions to oral ingestion of salicylates.[1] Dermal toxicity is described in the case literature as follows: dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug; following dermal application of a Salicylic Acid ointment in an elderly subject recovering from acute renal failure; topical application of Methyl Salicylate (and methanol) followed by the application of heat (skin and muscle necrosis and interstitial nephritis); and severe urticarial and angioedema with Methyl Salicylate exposure. In 20 patients with eczema or contact dermatitis, Methyl Salicylate at 67% is reported to cause irritation in 8 subjects; at 40%, 2 subjects;

and at 38%, 15%, and 3.75% - no irritation in any subject. In 2 case studies of reactions to a wart paint containing Salicylic Acid, Salicylic Acid (tested at 3% in petrolatum) was not the causative agent. Methyl Salicylate (2%) in arachis oil and 2% aqueous Sodium Salicylate produced positive patch results in a patient with acute dermatitis who had been using an ointment containing menthol and camphor. Methyl Salicylate (12%) and Salicylic Acid (5%) in yellow soft paraffin produced positive patch tests in 4 patients with dermatitis and one with psoriasis, all with some history of exposure to salicylates.

Other Clinical Reports

Dermal

Salicylic Acid

In patients with venous leg eczema, Salicylic Acid augmented histidine release in 3/320 challenged with ragweed pollen.[1] Salicylic Acid exacerbated urticarial reactions to aspirin; 13 of 18 patients in one study and 6 of 20 in another. At 5% in petrolatum, however, Salicylic Acid did not cause any urticarial reactions in atopic, urticarial, non-atopic, and non-allergic patients. Salicylic Acid is well-documented to have keratolytic action on normal human skin. It had a small therapeutic effect in patients with various forms of ichthyosiform dermatoses, but decreased clearing in 8 of 11 psoriasis patients when compared to UV therapy alone. Therapeutic toxicities include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, skin eruptions, and fever. One estimate is that a blood concentration > 300 μg/mL of a salicylate should be considered toxic. Toxic reactions occur more frequently in children. Care must be taken in prescribing salicylate-containing medications because systemic clearance of salicylates may be reduced with age. Severe poisoning can result in delirium, hallucinations, convulsions, coma, and respiratory or cardiovascular collapse. Reversible hearing loss and tinnitus are reported side effects of salicylates at therapeutic levels.

A clinical trial was conducted using 34 patients with mild to moderate acne who were selected for treatment with supramolecular Salicylic Acid and benzoyl peroxide + adapalene gel.[99] The authors noted that the following factors greatly limit the application of Salicylic Acid as an anti-acne agent: (1) Salicylic Acid is poorly soluble in water and tends to precipitate out in a low-pH alcoholic solution. (2) The re-crystallization of Salicylic Acid in the formulation not only decreases the bioavailability of the active ingredient, but also leads to skin irritation. (3) Salicylic Acid (2%; pH range: 2.5-2.8) tends to cause skin irritation upon application to the skin. Thus, in order to overcome technical difficulties, the authors noted that a supramolecular approach was developed to selectively self-assemble the poorly water-soluble Salicylic Acid into water-soluble, organized entities in the form of intermolecular complexes. This technology uses reversible and non-covalent bonding to form a water-soluble supramolecular Salicylic Acid complex, which results in a slow release upon application, achieves maximum efficacy in low pH, and reduces skin irritation. In this clinical trial, a 2% supramolecular Salicylic Acid cream (hydrogel) was applied randomLy to one side of the face for 28 days. Benzoyl peroxide (5%) + 0.1% adapalene gel was applied to the other side of the face according to the same procedure. Common side effects, such as desquamation, dryness, burning, erythema, and pruritus were recorded and classified into mild, moderate, and severe grades. Three patients withdrew from the study due to the irritant contact dermatitis that was induced by benzoyl peroxide. There was no evidence of side effects to the 2% supramolecular Salicylic Acid cream.

Oral

Methyl Salicylate

Methyl Salicylate taken in quantities greater than or equal to 1 teaspoon are reported to be quite toxic (equivalent of the salicylate that could be derived from 20+ adult aspirin tablets.[1] Accidental poisoning is not uncommon, especially in children; symptoms of poisoning include kidney irritation, vomiting, and convulsions. The average lethal dose of Methyl Salicylate is 10 mL for children and 30 mL for adults.

Other

Sodium Salicylate

Sodium Salicylate injected in the skin of aspirin intolerant individuals affected several parameters as follows: 1/23 had a positive skin test to Sodium Salicylate; 2/31 were positive in the passive cutaneous anaphylaxis test; and 2/26 were positive in the lymphocyte transformation test.[1]

Salicylates

A review of radiographs taken in 155 cases of juvenile arthritis in which various forms of salicylates had been administered (method not stated) at concentrations ranging from 0.1 to 3.24 g for several months did not find any evidence of bone lesions.[1]

RIFM SAFETY ASSESSMENT CONCLUSION ON SALICYLATES

A published toxicologic and dermatologic assessment of salicylates used as fragrance ingredients is available from the Research Institute for Fragrance Materials (RIFM).[100] The RIFM Expert Panel concluded that, "based on the available data, and using the NOAEL values of 50 mg/kg body weight/day identified in subchronic and chronic toxicity studies, a MOS for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of product use and bioavailability following dermal application) times the maximum daily exposure." This conclusion is based on a review of safety test data on salicylates that were available before and after publication of the initial CIR published final report on salicylates. Many of the studies are found in the original CIR Final Report on salicylates and in this report. Studies on salicylates with aromatic sidechains (i.e., Benzyl Salicylate) are also mentioned in the RIFM safety assessment conclusion. CIR is conducting a separate safety assessment of Benzyl Salicylate; therefore, such studies (on salicylates with aromatic sidechains) are not included in this re-review document or the original CIR Final Report, and are not relevant to this safety assessment. It should be noted that RIFM's conclusion should not be considered alone, but along with the more recent data summaries that are included in this report.

SUMMARY

The Panel published a Final Report on the Safety Assessment of Salicylic Acid and 16 salicylates in 2003. In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years; because the Panel determined that the original conclusion needed to be reconsidered, a re-review was completed. MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus, it is not included in this re-review.

The Final Report was reopened to revise the Panel's original conclusion and to add 3 structurally similar ingredients (Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate). Thus, this re-review document relates to the ingredients in that original report (except MEA-Salicylate), as well as 3 additional salicylates that have been added to the safety assessment. Furthermore, at the time of the original safety assessment, Capryloyl Salicylic Acid was defined as an ester. This was a mistake that has been corrected. Based on the correct structure, it was determined that Capryloyl Salicylic Acid does not belong in this report.

Of the 18 ingredients that are included herein, the greatest reported use frequency of 3974 uses is for Ethylhexyl Salicylate. The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest reported maximum use concentration for the salicylates that are being in this safety assessment. Salicylic Acid is used in peels (rinse-off products) at concentrations up to 30%.

In vitro skin penetration data (human or rat skin) indicated that Ethylhexyl Salicylate and Methyl Salicylate were percutaneously absorbed. The results from another in vitro skin penetration study on Ethylhexyl Salicylate and Salicylic Acid involving human skin indicated that the skin permeability of both ingredients was relatively low. Additionally, the conversion of Methyl Salicylate to Salicylic Acid in hairless mouse skin in vitro following topical application of 1% Methyl to the skin was evaluated. Less than 5% of applied dose was metabolized to Salicylic Acid. In an in vitro percutaneous absorption study (porcine skin) on Salicylic Acid, 34.48% dermal absorption was reported. A dermal absorption value of 40.05% for Salicylic Acid was reported in another in vitro study in which [^{14}C]-Salicylic Acid was applied to porcine skin. The in vitro percutaneous absorption of [^{14}C]-Salicylic Acid was also evaluated using human abdominal skin samples (split-thickness). Study results provided a high-end estimate of skin absorption (worst case) of $50.09 \pm 5.12\%$. When [^{14}C]-Salicylic Acid was applied to cadaverous skin in vitro, the total amount of [^{14}C]-Salicylic Acid absorbed in the skin (epidermis + dermis + receptor fluid) as a percent of the applied dose increased from 4.5% without occlusion, to 50.5% under 8 h of occlusion.

In an in vitro study on human placental absorption, Salicylic Acid (8 µg/mL) was dissolved into the maternal perfusate on the maternal side of the placenta. Results indicated the potential for Salicylic Acid to cross the placenta.

In in vivo studies, the percutaneous absorption of Methyl Salicylate has been demonstrated in pigs and humans, and the percutaneous absorption of Ethylhexyl Salicylate has been demonstrated in humans. The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using male Wistar rats. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/mL throughout the study period. A mathematical method was used to estimate total body absorption of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate. The estimated total body absorption (skin area) values at 12 h were: 3.3 µg/1.4 m^2 (Ethylhexyl Salicylate), 27 µg/1.4 m^2 (Hexyl Salicylate), and 13,000 µg/1.4 m^2 (Methyl Salicylate). Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid. After oral administration, Salicylic Acid is well absorbed from the gastrointestinal tract and is rapidly distributed throughout the extracellular fluid and most tissues. High concentrations (not specified) are found in the liver and kidneys; and, 50% to 80% of Salicylic Acid in the plasma is bound to albumin and other proteins.

In acute dermal toxicity studies of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate involving rabbits, the LD$_{50}$ was > 5 g/kg for each salicylate. No signs of systemic toxicity were observed in rabbits after application of Salicylic Acid (0.5 g, moistened with 0.5 mL water) to the skin. An acute dermal LD$_{50}$ of > 2 g/kg was reported for Sodium Salicylate in a study involving rats. An acute oral LD$_{50}$ of > 5 g/kg for Ethylhexyl Salicylate and Hexyl Salicylate in studies involving rats has also been reported. In acute oral toxicity studies on Methyl Salicylate involving mice, the LD$_{50}$ was calculated to be 1.39 g/kg (95% CI of 1.25 to 1.54 g/kg) and a dose of 0.5 g/kg was selected as the maximum tolerated dose. LD$_{50}$ values in the range of 0.5 to 2 g/kg were reported following administration of a single oral dose of Salicylic Acid (in gum Arabic) to rats. The mean oral lethal dose of Sodium Salicylate in male and female Wistar rats was considered to be > 0.2 g/kg to ≤ 2 g/kg. In an acute inhalation toxicity study on Salicylic Acid involving rats, no significant gross pathological changes were observed and the 1-h LC$_{50}$ was > 0.9 mg/l.

None of the rabbits died and there were no visible abnormalities at necropsy in a short-term dermal toxicity study on Salicylic Acid (in 8% propylene glycol butyl ether in ethanol). A 150 mg/kg/day dose of a Butyloctyl Salicylate trade name material was considered the NOEL in a short-tern oral toxicity study involving rats. The highest dose (1000 mg/kg/day) caused an increase in in mean prothrombin and activated partial thromboplastin times, but no macroscopic or microscopic pathological changes. In a short-term inhalation toxicity study involving mice, there were no test substance-related gross pathological or histopathological findings after inhalation of a fragrance mixture containing 5.8% Amyl Salicylate. Also, in a short-term inhalation toxicity study evaluating respiratory sensitization potential, Methyl Salicylate did not induce a measurable IL-4 response. There were no test substance-related gross pathological or histopathological findings in rats in a subchronic inhalation toxicity study of a fragrance mixture containing 4% Amyl Salicylate.

Two subchronic dermal studies involving rabbits were performed to evaluate the cutaneous and systemic toxicity of 2 cleansing formulations diluted to 0.25 % Salicylic Acid (dose volume of 2 mL/kg; dose = 10 mg/kg). Repeated applications were made. None of the animals died, and histopathological examinations provided no evidence of systemic toxicity. Another subchronic study using rabbits involved topical doses up to 120 mg/kg Salicylic Acid. None of the animals died, but a low incidence of trace to mild myocardial degeneration was observed in all dose groups and in the vehicle control group at histopathological examination; there was no dose-response relationship for this finding.

In an in vitro developmental toxicity study involving Salicylic Acid, post-implantation rat embryos were cultured with Salicylic Acid concentrations of 10 to 1000 µg/mL. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner. The same results were reported for rat embryos cultured with Salicylic Acid or Sodium Salicylate at concentrations in the 0.1 to 0.6 mg/mL range. Because of the reduced absolute body weights of pups from the 250 mg/kg/day dose group in an oral developmental toxicity study involving rats, the NOEL for developmental toxicity of Ethylhexyl Salicylate was considered to be the lower dose of 80 mg/kg/day. Another developmental toxicity study on Ethylhexyl Salicylate was performed according to the same test procedure. Based on observations of increased post-implantation loss, reduction in the gestation index, and lower litter size, the NOAEL for developmental toxicity was determined to be 25 mg/kg/day. On postnatal day 1, 89% of the pups from dams (rats) that had received a single oral dose of 300 mg/kg Sodium Salicylate had supernumerary ribs. No external malformations of pups were observed. In another study, a 4.8% incidence of malformations (including exencephaly and spina bifida) was reported for fetuses from rats dosed with Sodium Salicylate (250 mg/kg/day) on gestation days 8 to 10. It has been reported that the use of Salicylic Acid in the third trimester can potentially cause closure of the ductus arteriosus and oligohydramnios.

Salicylic Acid was not genotoxic in the in vitro mouse lymphoma assay at doses up to 1400 µg/mL, with or without metabolic activation. In a mammalian cell genotoxicity test involving CHO cells, Sodium Salicylate was not genotoxic over the range of concentrations tested (0.06 to 0.5 mM), with or without metabolic activation.

Hairless mice were evaluated for skin cancer in a study in which the effects of synthetic solar light on the skin after application of a cream containing 2% or 4% Salicylic Acid were evaluated. It was concluded that Salicylic Acid had a protective effect against the photocarcinogenicity of light at lower intensities.

In an estrogen receptor binding study using a consensus modeling method, Ethylhexyl Salicylate was classified as an estrogen receptor non-binder, whereas Butyloctyl Salicylate was classified as having binding activity to the estrogen receptor. When the estrogenic activity of Ethylhexyl Salicylate was compared to 17-ß-estradiol in a recombinant yeast estrogen assay, the dose response curve for Ethylhexyl Salicylate was shallower than the one for 17-ß-estradiol and Ethylhexyl Salicylate had a submaximal response for estrogenic activity.

Undiluted Amyl Salicylate (0.1 g) was severely irritating to the skin of rabbits, but mildly irritating to the skin of guinea pigs. Undiluted Amyl Salicylate (0.05 g) did not cause skin irritation in miniature swine. Mild erythema was observed in the acute dermal toxicity study on Ethylhexyl Salicylate that is summarized in this safety assessment. In another test, the application of undiluted Ethylhexyl Salicylate to the skin of rabbits did not result in skin irritation.

Following intradermal injection, 0.1% Hexyl Salicylate (vehicle not reported) produced an irritation reaction in guinea pigs, but 5% Hexyl Salicylate (vehicle not reported) did not. An explanation for these results was not provided. In an irritation test in which patches containing up to 2% Hexyl Salicylate (0.1 mL) were applied to Dunkin/Hartley albino guinea pigs, slight erythema and edema were observed at concentrations of 0.25%, 0.5%, 1%, and 2%; very slight erythema was observed at a concentration of 0.1%. Patches saturated with concentrations up to 50% Hexyl Salicylate were applied to Dunkin/Hartley albino guinea pigs in another test, and slight skin irritation was observed at concentrations of 25% and 50%, but not 10%. The patch testing of hairless guinea pigs with Hexyl Salicylate (0.3 mL per patch) at concentrations up to 100% yielded negative results. Skin irritation also was not observed in miniature swine tested with undiluted Hexyl Salicylate (20 µl/5 cm^2). When the irritation potential of Hexyl Salicylate at concentrations up to 100% was evaluated using rabbits, patch test (0.5 mL per patch) results for 10%, 25%, 50%, and 100% Hexyl Salicylate were negative. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on Hexyl Salicylate that is summarized in this safety assessment. Skin irritation was not observed in hairless mice tested with Hexyl Salicylate (20 µl/5 cm^2).

In a study in which Methyl Salicylate was applied to the skin of rabbits at concentrations up to 100%, skin irritation was observed only at concentrations of 25% and 100%. Flaking, hyperkeratosis, and dry desquamation were observed after an aliquot of 20 µl of undiluted wintergreen oil (contained 80 to 99% Methyl Salicylate) was applied to miniature swine. When Methyl Salicylate was applied repeatedly (twenty-one 0.1 mL applications) to guinea pigs in an open epicutaneous test, the minimal irritating concentration was determined to be 3% Methyl Salicylate. A minimally irritating concentration of 20% was determined in a skin irritation test on Methyl Salicylate. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on 5 g/kg Methyl Salicylate that is summarized in this safety assessment. Mixed results were observed in irritation studies of Salicylic Acid. When Salicylic Acid (0.5 g in water) was applied to the skin of rabbits, there was no evidence of skin irritation. Salicylic Acid was irritating to the skin of rabbits at concentrations of 10% and 25%. The single application of alcoholic solutions containing 2% Salicylic Acid to the skin of rabbits resulted in mild to no skin irritation. Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs caused mild skin irritation. In skin irritation tests on 2 cleansing formulations containing 0.5% Salicylic Acid, the undiluted product or the product diluted to a concentration of 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) was applied repeatedly to the skin of rabbits. The products tested were considered slightly and transiently irritating to the skin when applied undiluted or diluted to a concentration of 50%. Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol were applied repeatedly to the skin of rabbits. The formulations were classified as skin irritants. Sodium Salicylate (0.5 g in water) was non-irritating to the skin of rabbits.

Skin irritation was not observed in a 48-h occlusive patch test on 32% Amyl Salicylate (in acetone) involving 50 subjects. Skin irritation also was not observed in a 48-h closed patch test on 4% Ethylhexyl Salicylate (in petrolatum) involving 23 subjects. Using Hilltop® chambers on 30% Hexyl Salicylate involving 103 subjects, skin irritation was not observed. Skin irritation also was not observed in a 48-h patch test on 3% Hexyl Salicylate involving 22 subjects, in a 4-h patch (Hilltop® chamber) test on undiluted Hexyl Salicylate involving 30 subjects, or in a 24-h patch (Hilltop® chamber) test on Hexyl Salicylate at concentrations up to 30% in a study involving 56 subjects.

Skin irritation was not observed in a 48-h occlusive patch test involving 27 subjects or in a 48-h occlusive patch test on 12% wintergreen oil (containing 80 to 99% Methyl Salicylate) involving 25 subjects. In a study evaluating the skin irritation potential of Methyl Salicylate (in 80% ethanol and 20% deionized water) pipetted (25 mL) onto the skin of 9 subjects, 30% and 60% Methyl Salicylate caused skin irritation. It has been noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus. A potential for skin irritation was demonstrated in a cumulative irritation study in which a shampoo containing 3% Salicylic Acid was applied (as a 4% dilution) continuously, under a patch, to human subjects (number not stated). Exaggerated use repeated application tests (4 studies; number of subjects not stated) were performed to compare shampoos (prototype or commercial formulations) containing 3% Salicylic Acid and shampoo formulations containing up to 2% Salicylic Acid with a placebo). Results

indicated no statistically significant differences in combined irritation or TEWL. A cream containing 2% Salicylic Acid was classified as non-irritating when applied repeatedly to the skin of human subjects.

A surfactant-based product containing 2% Salicylic Acid (pH of 3.8; diluted concentration not stated) was mildly irritating when applied repeatedly to the skin of human subjects (number not stated).   In another test, the same product was classified as probably mildly irritating under normal use conditions. Daily applications of a hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82) to the skin of human subjects (number not stated) did not result in skin irritation. When a hydroalcoholic gel containing 2% Salicylic Acid was applied repeatedly to the skin of human subjects (number not stated), slight skin irritation was observed. Two creams containing 2% Salicylic Acid (each in a separate test) were applied repeatedly to the skin of human subjects (number not stated). One cream was classified as non-irritating, and the other was classified as moderately irritating. In a repeated open application test, a cream containing 2% Salicylic Acid was applied to the backs of human subjects (number not stated). The cream did not cause reactions that were different from those induced by the control. In a home use test, a non-alcoholic lotion containing 2% Salicylic Acid caused mild, transient reactions when applied repeatedly to the skin of human subjects (number not stated). In second home use test involving human subjects (number not stated; 50% had sensitive skin), repeated applications of a non-alcoholic cream containing 2% Salicylic Acid caused little or no skin irritation. In a third home use test involving 194 human subjects, non-alcoholic lotions and moisturizers containing 2% Salicylic Acid (pH 2.28) caused itching, stinging, mild erythema, and burning. Repeated applications of a cream containing 1.5 % Salicylic to the skin of human subjects (number not stated) for 21 days caused slight skin irritation.

Formulations containing up to 7.5% Salicylic Acid were applied to groups of 6 rabbits. The 3.5%, 5%, and 7.5% formulations caused desquamation, an inflammatory reaction, and a comedogenic effect.

Hexyl Salicylate was predicted to be a skin sensitizer in the Genomic Allergen Rapid Detection assay. Using an integrated testing strategy for skin sensitization that focuses on 3 in vitro methods that cover the first 3 steps of the adverse outcome pathway, results for the sensitization potential of Salicylic Acid were considered equivocal, but ultimately were considered positive results.

In the LLNA, a very low EC3 value (0.18%) was reported for Hexyl Salicylate, which may have been due to possibly sensitizing impurities. When Hexyl Salicylate was tested for sensitization potential in guinea pigs using a modified Draize procedure, sensitization was observed after intradermal challenge with 0.1% Hexyl Salicylate and topical challenge with 5% Hexyl Salicylate.   In a photoallergy test involving hairless albino guinea pigs, sensitization reactions were not observed after challenge with 50% and 100% Hexyl Salicylate. In a Magnusson-Kligman guinea pig maximization test, skin sensitization was not observed in guinea pigs challenged with 10% Hexyl Salicylate in acetone.

Methyl Salicylate (50%) was predicted to be a non-sensitizer in the LLNA. The same was true for Salicylic Acid (concentration not stated) and 0.7 µM Methyl Salicylate. In a modified Buehler test, Methyl Salicylate (25% w/v in hydro-alcoholic solution) did not cause skin sensitization in a group of 20 guinea pigs. The same was true for Salicylic Acid (25% w/v in hydro-alcoholic solution) when tested according to the same procedure.

Neither skin irritation nor sensitization was observed in an HRIPT in which 52 subjects were patch tested with undiluted Butyloctyl Salicylate. A human skin sensitization NOEL of 35,433 µg/cm^2 (study details not provided) has been reported for Hexyl Salicylate. Also, in a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 µg/cm^2 (study details not included). In an HRIPT (Hilltop® chamber system) involving 103 subjects, sensitization reactions to 30% Hexyl Salicylate were not observed. Maximization test results for 3% Hexyl Salicylate in petrolatum were negative in 22 subjects.

In a human maximization test on wintergreen oil (contains 80 to 99% Methyl Salicylate) involving 25 volunteers, sensitization was not observed at a concentration of 12%. Maximization test results for 8% Methyl Salicylate were also negative in 27 subjects. In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate did not induce skin sensitization. Product formulations containing 2% Salicylic Acid did not cause sensitization in HRIPTs (test populations: 84 to 198 subjects).

Amyl Salicylate was classified as a non-sensitizer in a QSAR system for estimating sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and their activated metabolites to react with skin proteins.   Hexyl Salicylate and Methyl Salicylate were classified as non-allergenic in a study that was performed to validate a QSAR rank model for grading allergenic potency. An exposure-based QRA methodology has been used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate. Limitations for various finished product categories have been established, ranging from 1.3% to 25.7%.

Results for Ethylhexyl Salicylate were classified as negative in the 3T3 neutral red uptake phototoxicity test at concentrations ranging from 0.1 to 316 µg/mL. Undiluted Hexyl Salicylate was not phototoxic in studies involving mice or miniature swine. At concentrations ranging from 5% to 100%, Hexyl Salicylate was not phototoxic to albino hairless guinea pigs. Hexyl Salicylate did not induce photoallergenicity in groups of albino hairless guinea pigs tested with concentrations of 50% and 100%.

The phototoxicity of undiluted wintergreen oil (contained 80% to 99% Methyl Salicylate) was evaluated using miniature swine, and results were negative. Methyl Salicylate (50% in diethyl phthalate) was evaluated for phototoxicity and photoallergenicity potential using 25 guinea pigs. Both evaluations involved exposure to UVA and UVB light, and the test substance was classified as non-phototoxic and non-photoallergenic. There also was no evidence of phototoxicity in 56 subjects tested with Hexyl Salicylate at concentrations of 0.3%, 3%, and 30%.

Sodium Salicylate was classified as an ocular irritant using the EpiOcular^{TM} reconstructed human cornea-like tissue model, whereby the tissues were incubated with 50 µl of Sodium Salicylate. Undiluted Ethylhexyl Salicylate was classified as a non-irritant in an ocular irritation study involving rabbits. In an ocular irritation test involving rabbits, the instillation of Methyl Salicylate (0.0005 mL) caused a grade 3 reaction (necrosis on 13 to 37% of the cornea). Intense conjunctival irritation, accompanied by chemosis and considerable discharge, was observed in rabbits in which 1.25% Methyl Salicylate (0.1 mL) was instilled into the eyes. Salicylic Acid (purity not stated) caused severe ocular irritation in rabbits. Numerous formulations (non-alcoholic and hydroalcoholic) that contained Salicylic Acid at concentrations ranging from 0.05% to 2% have been evaluated in the Draize test (rabbits). The investigators considered these formulations to be mild irritants when instilled into the eyes of rabbits. Sodium Salicylate was classified as mildly irritating to the eyes of rabbits.

In multicenter studies, an irritant or doubtful reaction was observed in 2 of 1323 patients patch (Finn chamber) tested with 1% Amyl Salicylate and 3 positive reactions and 5 doubtful reactions were observed in a population of 1855 patients patch tested with 5% Amyl Salicylate. No reactions were observed in a multicenter study in which 218 fragrance-sensitive patients with contact dermatitis were patch tested with 5% Hexyl Salicylate.

Positive patch test reactions to 2% and 5% Ethylhexyl Salicylate were reported in another case report (patient with facial telangiectasia and history of rosacea), but reactions to these test concentrations were negative in the 29 consecutive eczema patients that served as controls. Also, patch test reactions to the following salicylates were negative in this case report: 5% Amyl Salicylate, 2% Methyl Salicylate, 2% Salicylic Acid, and 2% Sodium Salicylate. A contact dermatitis patient had a positive patch test reaction to Ethylhexyl Salicylate (concentration not stated), but not to Salicylic Acid, Methyl Salicylate, or Sodium Salicylate. Topical Salicylic Acid hypersensitivity (pain and swelling of digits) was observed in a woman with no known allergies after use of OTC topical Salicylic Acid for the treatment of warts. In a clinical trial involving 34 patients with mild to moderate acne, repeated applications of a 2% supramolecular Salicylic Acid cream (hydrogel) did not result in any adverse effects on the skin.

Due to concern over the potential reproductive toxicity of Salicylic Acid in humans, MOS calculations taking into consideration maximum use concentrations of this ingredient in rinse-off and leave-on cosmetic products were performed. The calculations yielded MOS values of 370 and 432 for rinse-off products containing 30% Salicylic Acid (actual exposure measurements were used for the 30% Salicylic Acid peel product) and a MOS of 177 for leave-on products (body lotion + face cream + hand cream) containing up to 2% Salicylic Acid. An additional risk assessment was performed because the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds the IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products of all types. A MOS of 220 was calculated in this risk assessment.

In a toxicological and dermatological assessment of salicylates when used as fragrance ingredients, performed by RIFM, a MOS for systemic exposure is mentioned. Based on NOAEL values of 50 mg/kg body weight/day in subchronic and chronic toxicity studies, a MOS for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of bioavailability and product use following dermal application) times the maximum daily exposure.

DISCUSSION

In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. MEA-Salicylate was previously rereviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus, it is not included in this rereview. Because the structure of Capryloyl Salicylic was originally mischaracterized, it is also not included in this rereview and will be reassessed elsewhere. After reviewing the available new data on ingredients included in the original safety assessment, as well as all the available data on the 3 additional structurally

similar salicylates (Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate) that are now included in the grouping, the Panel re-opened the report to revise the original conclusion, remove the qualification relating to formulating products to avoid increasing the skin's sun sensitivity, and add the 3 additional salicylates. The qualification regarding sun sensitivity was removed based on results from an NTP photocarcinogenicity study indicating that Salicylic Acid has some protective effect against photocarcinogenicity, at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

The Panel expressed concern over the reproductive toxicity of Salicylic Acid, having considered that, in the third trimester, the use of Salicylic Acid can potentially cause early closure of the ductus arteriosus and oligohydramnios. Thus, the Panel requested that CIR calculate an MOS for Salicylic Acid exposure, taking into consideration the extent of dermal absorption during cosmetic product use (at the highest maximum use concentration in leave-on products). Because the highest reported maximum use concentration of Salicylic Acid in cosmetic products is 30% in a rinse-off product (peel) and the highest reported maximum use concentration of Salicylic Acid in leave-on products is 2% (face and neck products), it was determined that the MOS calculations should involve these two concentrations. Furthermore, given the potential for whole-body exposure during the application of body and hand products (leave-on products) containing a highest maximum use concentration of 0.2% Salicylic Acid, it was determined that this concentration should also be included in the MOS calculation.

For the 30% peel product, two MOS were calculated. One compared the mean plasma Salicylic Acid concentration following application of the product to blood concentrations of salicylate that are considered toxic, and the other was a comparison to blood concentrations associated with salicylism. The calculations yielded MOS values of 370 and 432, respectively. An MOS of 177 was calculated for the combination of leave-on products containing 0.2% or 2% Salicylic Acid (body lotion (0.2%) + face cream (2%) + hand cream (0.2%)). These wide margins of safety ensure that exposure to Salicylic Acid at use concentrations in rinse-off or leave-on cosmetic products would not result in reproductive or developmental toxicity.

An additional risk assessment was performed because the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds IFRA's 1% concentration limit (relative to sensitization potential) for Hexyl Salicylate in lip products of all types. For this additional risk assessment, 100% absorption was assumed with application of a lipstick containing 35.9% Butyloctyl Salicylate, and an MOS of 220 was calculated. This wide margin of safety ensures that exposure to Salicylic Acid at use concentrations in lipsticks would not induce sensitization.

The Panel acknowledged positive sensitization data on the salicylates and noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application. Thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using salicylates. The Panel also specified that products containing salicylates must be formulated to be non-irritating.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council's survey results indicate that the highest maximum ingredient use concentration in a spray product is being reported for Ethylhexyl Salicylate, which is used in suntan aerosol and pump sprays at concentrations up to 5%. Also, Salicylic Acid is being used in suntan product pump sprays at concentrations up to 0.5%. The highest maximum ingredient use concentration in a powder is being reported for Butyloctyl Salicylate, which is being used at concentrations up to 3.6% in face powders. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA):

Salicylic Acid	Isodecyl Salicylate
Amyl Salicylate	Isotridecyl Salicylate*
Butyloctyl Salicylate	Magnesium Salicylate
Calcium Salicylate*	Methyl Salicylate
C12-15 Alkyl Salicylate*	Myristyl Salicylate*
Ethylhexyl Salicylate	Potassium Salicylate*
Hexyl Salicylate	Sodium Salicylate
Hexyldodecyl Salicylate*	TEA-Salicylate
Isocetyl Salicylate*	Tridecyl Salicylate

Not reported to be in current use. Were the ingredient in this group not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; CIR Staff]
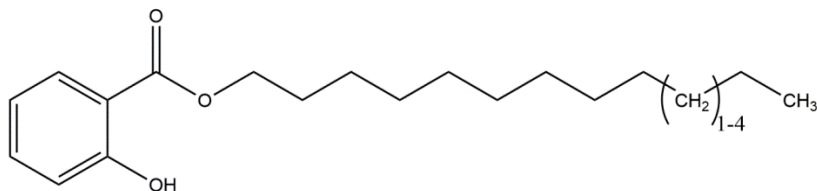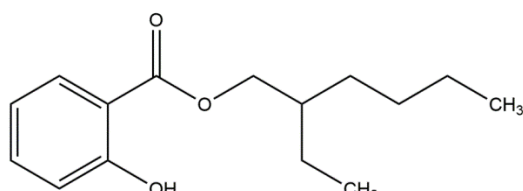
Ingredient CAS No.	Definition & Structures	Function(s)
Salicylic Acid 69-72-7	Salicylic Acid is the aromatic acid that conforms to the formula:	Antiacne Agents; Antidandruff Agents; Corn/Callus/Wart Removers; Denaturants; Exfoliants; Fragrance Ingredients; Hair Conditioning Agents; Hair-Waving/Straightening Agents; Skin-Conditioning Agents - Miscellaneous
Amyl Salicylate 2050-08-0	Amyl Salicylate is the ester of amyl alcohol and Salicylic Acid that conforms to the formula:	Fragrance Ingredients
Butyloctyl Salicylate 190085-41-7	Butyloctyl Salicylate is the organic compound that conforms to the formula:	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Calcium Salicylate 824-35-1	Calcium Salicylate is the calcium salt of Salicylic Acid that conforms to the formula:	Preservatives
C12-15 Alkyl Salicylate	C12-15 Alkyl Salicylate is the ester of C12-15 alcohols and salicylic acid. It conforms generally to the formula: where R represents the C12-15 alkyl group.	Skin-Conditioning Agents - Miscellaneous
Ethylhexyl Salicylate 118-60-5	Ethylhexyl Salicylate is the ester of 2-ethylhexyl alcohol and Salicylic Acid. It conforms to the formula:	Fragrance Ingredients; Light Stabilizers; Sunscreen Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; CIR Staff]
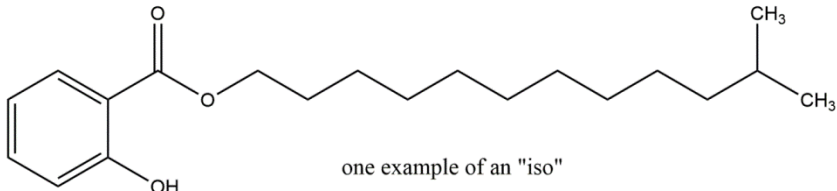
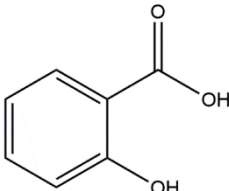| Ingredient CAS No.	Definition & Structures	Function(s)
Hexyl Salicylate 6259-76-3	Hexyl Salicylate is the organic compound that conforms to the formula:	Fragrance Ingredients; Skin-Conditioning Agents - Occlusive
Hexyldodecyl Salicylate 220778-06-3	Hexyldodecyl Salicylate is the organic compound that conforms to the formula:	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Isocetyl Salicylate 138208-68-1	Isocetyl Salicylate is the ester of Isocetyl Alcohol and Salicylic Acid. It conforms to the formula: one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Isodecyl Salicylate 85252-25-1	Isodecyl Salicylate is the ester of branched chain decyl alcohols and Salicylic Acid that conforms to the formula: one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Isotridecyl Salicylate 1863871-63-9	Isotridecyl Salicylate is the organic compound that conforms to the formula: one example of an "iso"	Antistatic Agents; Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; CIR Staff]
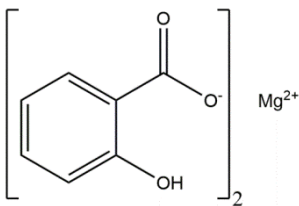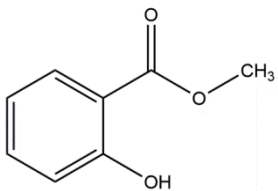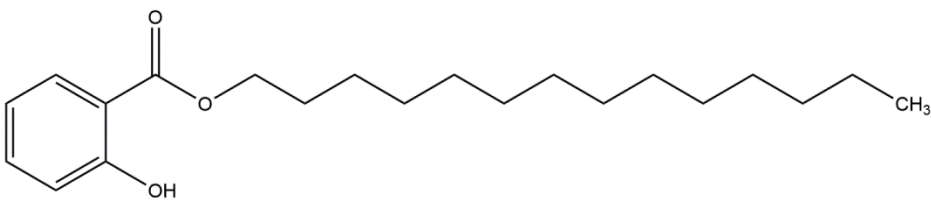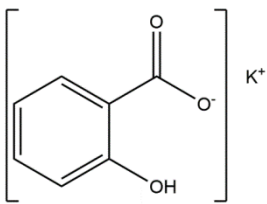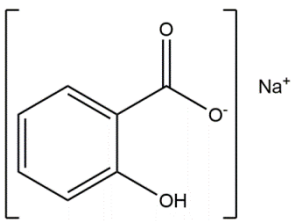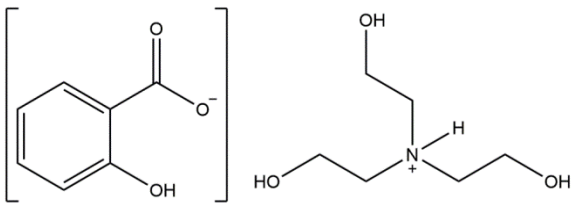
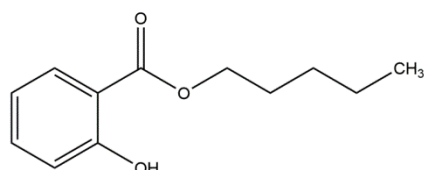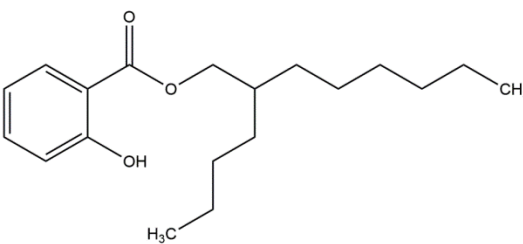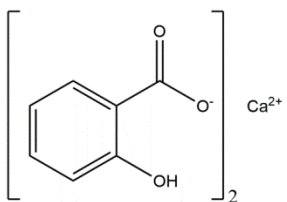| Ingredient CAS No.	Definition & Structures	Function(s)
Magnesium Salicylate 18917-89-0 551-37-1	Magnesium Salicylate is the magnesium salt of Salicylic Acid that conforms to the formula:	Preservatives
Methyl Salicylate 119-36-8	Methyl Salicylate is the ester of methyl alcohol and Salicylic Acid. It conforms to the formula:	Denaturants; External Analgesics; Flavoring Agents; Fragrance Ingredients; Oral Health Care Drugs
Myristyl Salicylate 19666-17-2	Myristyl Salicylate is the ester of myristyl alcohol and Salicylic Acid. It conforms to the formula:	Not Reported
Potassium Salicylate 578-36-9	Potassium Salicylate is the potassium salt of Salicylic Acid that conforms to the formula:	Cosmetic Biocides; Preservatives
Sodium Salicylate 54-21-7	Sodium Salicylate is the sodium salt of Salicylic Acid that conforms to the formula:	Denaturants; Preservatives
TEA-Salicylate 2174-16-5	TEA-Salicylate is the triethanolamine salt of Salicylic Acid that conforms generally to the formula:	Light Stabilizers; Sunscreen Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; CIR Staff]
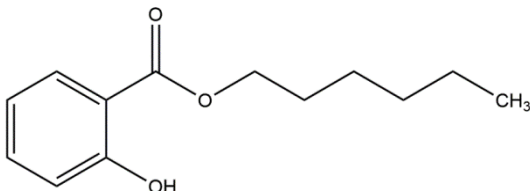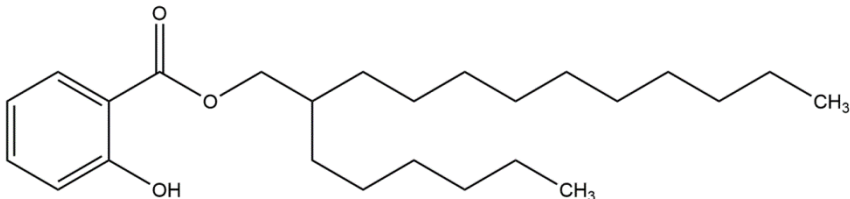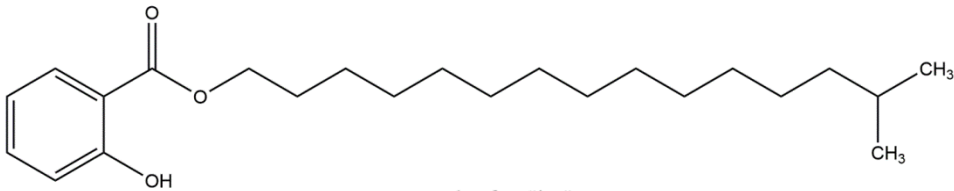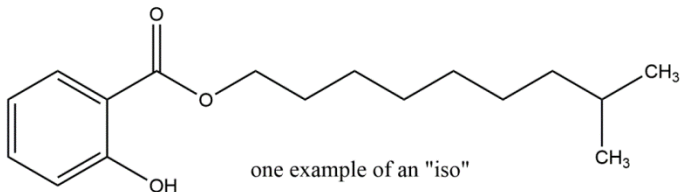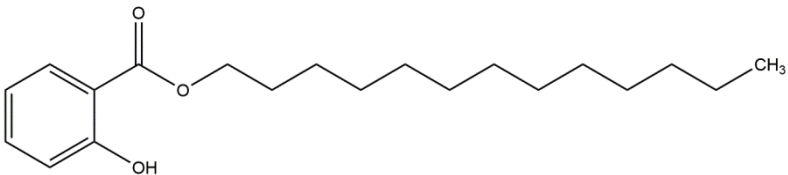
Ingredient CAS No.	Definition & Structures	Function(s)
Tridecyl Salicylate 19666-16-1	Tridecyl Salicylate is the ester of tridecyl alcohol and Salicylic Acid. It conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
Amyl Salicylate		
Molecular weight (Da)	208.26	10
Density (g/cm^3)	1.0552	12
Boiling point (ºC)	270	12
log P	3.12 (estimated)	10
pK$_a$	10.4 (estimated)	10
Butyloctyl Salicylate		
Molecular weight (Da)	306.45	10
log P	6.03 (estimated)	10
pK$_a$	10.3 (estimated)	10
Calcium Salicylate		
Formula weight (Da)	314.31	10
C12-15 Alkyl Salicylate		
Molecular weight (Da)	306.45 – 348.53	10
Ethylhexyl Salicylate		
Form	Colorless liquid	7
Molecular weight (Da)	250.34	10
Water solubility (mg/l at 25ºC)	0.7171 (estimated)	7
Vapor pressure (mm Hg at 25ºC)	0.00000436	7
Flash point (ºC)	> 200	7
log K$_{ow}$	6.02 (estimated)	7
Hexyl Salicylate		
Form	Colorless, oily liquid	8
Molecular weight (Da)	222.28	10
Water solubility (mg/l at 25ºC)	6.084 (estimated)	8
Vapor pressure (mm Hg at 20ºC)	< 0.001	8
Boiling Point (ºC)	> 200	8
Log K$_{ow}$	5.06 (estimated)	8
Hexyldodecyl Salicylate		
Molecular weight (Da)	390.61	10
Density (g/cm^3)	0.960 ± 0.06 (estimated)	12
Boiling point (ºC)	474.3 ± 18.0 (estimated)	12
log P	8.53 (estimated)	10
pK$_a$	10.3 (estimated)	10
Isocetyl Salicylate		
Molecular weight (Da)	326.55	10
log P	7.63 (estimated)	10
pK$_a$	10.4 (estimated)	10

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
Isodecyl Salicylate		
Molecular weight (Da)	278.39	[10]
log P	5.12 (estimated)	[10]
pK$_a$	10.4 (estimated)	[10]
Isotridecyl Salicylate		
Molecular weight (Da)	320.47	[10]
log P	6.37 (estimated)	[10]
pK$_a$	10.4 (estimated)	[10]
Magnesium Salicylate		
Formula weight (Da)	298.53	[10]
Methyl Salicylate		
Form	Clear, colorless liquid	[9]
Molecular weight (Da)	152.15	[10]
Specific gravity	1.18	[9]
Water solubility (mg/l at 25ºC)	1875 (estimated)	[9]
Vapor pressure (mm Hg at 25ºC)	0.09 (estimated)	[9]
Boiling point (ºC)	222	[9]
Flash point (ºF)	> 212	[9]
log K$_{ow}$	2.6 (estimated)	[9]
Myristyl Salicylate		
Molecular weight (Da)	334.50	[10]
log P	6.88 (estimated)	[10]
pK$_a$	10.4 (estimated)	[10]
Potassium Salicylate		
Formula weight (Da)	176.21	[10]
Salicylic Acid		
Molecular weight (Da)	138.12	[10]
Density (g/cm^3)	1.443	[12]
Melting point (ºC)	157-159	[12]
Boiling point (ºC)	211	[12]
log P	1.2 (estimated)	[10]
pK$_a$	3.01 (1st - carboxylic; estimated)	[10]
Sodium Salicylate		
Formula weight (Da)	160.10	[10]
Melting point (ºC)	213 (decomposes)	[12]
TEA Salicylate		
Formula weight (Da)	287.31	[10]
Tridecyl Salicylate		
Molecular weight (Da)	320.47	[10]
Density (g/cm^3)	0.989 ± 0.06 (estimated)	[12]
Boiling point (ºC)	4.11 ± 18.0 (estimated)	[12]
log P	6.46 (estimated)	[10]
pK$_a$	10.4 (estimated)	[10]

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Amyl Salicylate				**Butyloctyl Salicylate**			
	2019[17]	---	2018[18]	---	2019[17]	1998[1]	2018[18]	2000[1]
Totals*	**10**		*0.0023-0.26*		**28**	NR	*1-35.9*	*0.5-5*
Duration of Use								
Leave-On	*1*		*0.0023-0.23*		*27*	*NR*	*1-35.9*	*0.5-5*
Rinse-Off	*9*		*0.02-0.26*		*1*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	NR		*NR*		NR	NR	NR	NR
Eye Area	NR		NR		1	NR	3.6	NR
Incidental Ingestion	NR		NR		12	NR	35.9	NR
Incidental Inhalation-Spray	NR		0.0023-0.0058; 0.12[a]		6[a]; 3[b]	NR	1-3	4-5[a]
Incidental Inhalation-Powder	NR		NR		3[b]	NR	3.6	0.5
Dermal Contact	1		0.02-0.26		16	NR	1-10	0.5-5 NR
Deodorant (underarm)	NR		0.23		NR	NR	NR	NR
Hair - Non-Coloring	9		0.0023-0.12		NR	NR	NR	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	NR		0.26		12	NR	35.9	NR
Baby Products	NR		NR		NR	NR	NR	NR

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Ethylhexyl Salicylate				**Hexyl Salicylate**			
	2019[17]	1998[1]	2018[18]	2000[1]	2019[17]	---	2018[18]	---
Totals*	**3974**	**83**	**0.0003-5.1**	**0.001-8**	**8**		**0.013-0.52**	
Leave-On	*3164*	*80*	*0.0003-5.1*	*0.001-8*	*5*		*0.013-0.12*	
Rinse-Off	*795*	*3*	*0.001-0.21*	*0.001-0.005*	*3*		*0.032-0.52*	
Diluted for (Bath) Use	*15*	*NR*	*0.2*	*NR*	*NR*		*NR*	
Eye Area	3	NR	0.1	NR	NR		0.00074	
Incidental Ingestion	54	2	4-4.5	8	NR		NR	
Incidental Inhalation-Spray	2660; 182[a]; 90[b]	18;2[b]	0.00099-5; 0.012-0.05[a]	0.001-0.01; 0.001-5[b]	2;1[a]; 1[b]		0.013-0.023; 0.11[a]	
Incidental Inhalation-Powder	5; 90[b]	2[b]	NR	5; 0.001-5[b]	1[b]		NR	
Dermal Contact	3777	45	0.0003-5.1	0.5-5	5		0.02-0.52	
Deodorant (underarm)	6	NR	0.0016	NR	NR		0.097	
Hair - Non-Coloring	132	35	0.00099-0.2	0.001-0.01	NR		0.013-0.21	
Hair-Coloring	5	NR	0.012	NR	3		0.5	
Nail	6	1	0.15	0.1	NR		NR	
Mucous Membrane	774	2	0.0012-4.5	8	NR		0.52	
Baby Products	NR	NR	NR	NR	NR		NR	

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Isodecyl Salicylate				**Magnesium Salicylate**			
	2019[17]	1998[1]	2018[18]	2000[1]	2019[17]	1998[1]	2018[18]	2000[1]
Totals*	**20**	**3**	**2.5**	**NR**	**11**	**NR**	**0.2**	**NR**
Leave-On	*19*	*2*	*2.5*	*NR*	*11*	*NR*	*0.2*	*NR*
Rinse-Off	*1*	*1*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	1	NR	NR	NR	11	NR	0.2	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	11[a]; 7[b]	2[a]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	7[b]	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	20	3	2.5	NR	2	NR	0.2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure.

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Methyl Salicylate				**Salicylic Acid**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**34**	**25**	**0.00000006-1**	**0.0001-0.6**	**1429**	**107**	**0.00001-30**	**0.0008-3**
Leave-On	*18*	*4*	*0.0000013-1*	*0.02*	*665*	*62*	*0.00001-2*	*0.02-3*
Rinse-Off	*15*	*20*	*0.00000006-0.23*	*0.0001-0.6*	*760*	*45*	*0.01-30*	*0.0008-3*
Diluted for (Bath) Use	*1*	*1*	*0.0016*	*NR*	*4*	*NR*	*NR*	*NR*
Eye Area	NR	NR	0.0000013-0.000026	NR	26	2	0.00001-0.2	0.2-2
Incidental Ingestion	11	14	0.038-0.23	0.03-0.2	1	NR	NR	1
Incidental Inhalation-Spray	16[a]; 8[b]	1[b]	0.0000051-0.5; 0.000065-0.23[b]	0.1; 0.02-0.2[b]	5; 190[a]; 272[b]	3; 10[b]	0.1-0.5; 0.004-0.5[a]	0.02-3[b]
Incidental Inhalation-Powder	8[b]	1[b]	0.000065-0.23[b]	0.02-0.2[b]	7; 272[b]	1; 10[b]	NR	0.2-0.6; 0.02-3[b]
Dermal Contact	22	6	0.00000006-1	0.0001-0.6	1081	77	0.00001-30	0.0008-3
Deodorant (underarm)	NR	NR	NR	NR	6	1	NR	NR
Hair - Non-Coloring	1	3	0.0000051-0.0011	NR	297	28	0.004-4	0.002-0.2
Hair-Coloring	NR	NR	0.00000002	NR	40	2	0.015-0.1	0.1
Nail	NR	NR	NR	NR	3	NR	NR	0.2
Mucous Membrane	15	17	0.000018-0.23	0.0001-0.2	217	2	0.064-0.2	0.0008-2
Baby Products	1	NR	NR	NR	2	NR	NR	NR
	Sodium Salicylate				**TEA-Salicylate**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**186**	**7**	**0.0008-0.5**	**0.09-2**	**5**	**5**	**NR**	**0.0001-0.75**
Leave-On	*76*	*5*	*0.0015-0.1*	*2*	*4*	*5*	*NR*	*0.0001-0.75*
Rinse-Off	*108*	*2*	*0.0008-0.5*	*0.09-0.3*	*1*	*NR*	*NR*	*0.0002*
Diluted for (Bath) Use	*2*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	6	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	2	NR	0.09-0.2	NR	NR	NR	NR
Incidental Inhalation-Spray	13[a]; 41[b]	1[b]	NR	0.09-2[b]	NR	1[b]	NR	0.001[b]
Incidental Inhalation-Powder	41[b]	1[b]	NR	0.09-2[b]	NR	1[b]	NR	0.001[b]
Dermal Contact	175	3	0.0015-0.5	2	NR	5	NR	0.0001-0.75
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	2	0.0008-0.5	0.2	5	NR	NR	NR
Hair-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	94	2	0.25-0.37	0.09-0.2	NR	NR	NR	0.0002
Baby Products	NR	NR	0.31	NR	NR	NR	NR	NR
	Tridecyl Salicylate							
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**				
Totals*	**13**	**2**	**NR**	**0.01**				
Leave-On	*10*	*2*	*NR*	*0.01*				
Rinse-Off	*3*	*NR*	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*				
Eye Area	1	NR	NR	NR				
Incidental Ingestion	NR	NR	NR	NR				
Incidental Inhalation-Spray	3[a]; 4[b]	2[b]	NR	0.01[b]				
Incidental Inhalation-Powder	4[b]	2[b]	NR	0.01[b]				
Dermal Contact	13	2	NR	0.01				
Deodorant (underarm)	NR	NR	NR	NR				
Hair - Non-Coloring	NR	NR	NR	NR				
Hair-Coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	1	NR	NR	NR				
Baby Products	NR	NR	NR	NR				

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible that these products <u>may</u> be sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

NR - no reported use

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Irritation (Animal)			
Amyl Salicylate (undiluted)	6 Albino angora rabbits	Test substance (0.1 g) applied (using glass syringe) for 24 h to 3 x 3 cm area on dorsal surface. Plastic collar (25-cm diameter) wrapped around the neck. Application repeated 30 min after end of 24-h contact period. Reactions scored 24 h after first application and 48 h and 72 h after 2nd patch application	Amyl Salicylate was severely irritating.[70]
Amyl Salicylate (undiluted)	6 male Hartley guinea pigs	Same protocol, but application to dorsal, mid-lumbar region	Amyl Salicylate was mildly irritating.[70]
Amyl Salicylate (undiluted)	6 miniature swine of the Pitman-Moore Improved strain	Test substance (0.05 g) applied, under 15 mm diameter patch, to dorsal skin for 48 h.	Amyl Salicylate was a non-irritant.[70]
Ethylhexyl Salicylate (undiluted)	4 rabbits (strain not stated)	Test substance applied (under occlusion) to intact or abraded skin for 24 h.	Mild erythema, lasting 24 h, was observed.[7]
Ethylhexyl Salicylate (undiluted)	3 male New Zealand White rabbits.	A semiocclusive patch containing the test substance (0.5 mL) was applied for 3 min to an ~ 6 cm^2 area on the anterior left flank of each animal. Similarly, a semiocclusive patch containing the test substance was applied for 1 h to the anterior right flank and for 4 h to the posterior right flank. Untreated skin served as the control. Reactions scored at ~1 h, 24 h, 48 h, and 72 h after patch removal.	Slight erythema observed at sites exposed for 3 minutes and 1 h, and well-defined erythema observed at sites exposed for 4 h. The erythema observed in 2 rabbits had resolved within 24 h, and the erythema observed in the third rabbit had resolved by 48 h. No evidence of edema at application sites of any animals. The test substance was considered a non-irritant.[30]
Hexyl Salicylate (1 to 100%)	Groups of 5 male hrBR outbred hairless albino guinea pigs	Single 0.1 mL application at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or undiluted. Applied to dorsal skin using 25 mm Hilltop® chambers. Chambers removed after 2 h (± 15 min). Reactions scored at 1h and 4 h after removal and at 1, 2, and 3 days post-administration.	Skin irritation was not observed at any of the concentrations tested.[8]
Hexyl Salicylate (10 to 50%)	4 male albino Dunkin/Hartley guinea pigs	Topical treatment with 8 mm diameter filter paper patches saturated with 10%, 25%, or 50% Hexyl Salicylate (in acetone), using 1 mm aluminum patch test cups. Patch removal after 24 h, and reactions scored at 24 h and 48 h post-removal.	No evidence of skin irritation (at 10% concentration). Very slight erythema (at 25% and 50%, 3 animals).[8]
Hexyl Salicylate (5%)	4 inbred Hartley albino guinea pigs	Test substance (0.1 mL) injected intradermally into the shaved flank. Reactions read 24 h after injection.	Skin irritation was not observed.[75]
Hexyl Salicylate (0.1 to 2%, in 0.01% dodecyl-benzenesulfonate/saline)	4 male albino Dunkin/Hartley guinea pigs	Same protocol	Very slight erythema (at 0.1%) and slight erythema and edema (at 0.25%, 0.5%, 1%, and 2%).[8]
Hexyl Salicylate (0.1%)	4 inbred Hartley albino guinea pigs	Same protocol.	Skin irritation was observed.[75]
Hexyl Salicylate (undiluted)	2 miniature swine	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[8]
Hexyl Salicylate (10 to 100%)	3 or 4 female New Zealand white rabbits	Surgical lint square (2.5 cm^2) containing 0.5 mL of 10%, 25%, or 50% Hexyl Salicylate in diethyl phthalate, or undiluted ingredient. Lint square (semi-occlusive patch) placed on 6 cm^2 area of clipped, intact dorsal skin for 4h. Reactions assessed at 1 h, 24 h, 48 h, 72 h, and 168 h after patch removal.	Skin irritation was not observed at concentrations of 10% and 25%, but was observed at higher concentrations.[8]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Hexyl Salicylate (undiluted)	10 rabbits (strain not stated)	Single dermal dose of 5 g/kg [skin irritation data from acute dermal toxicity study]	Skin irritation was observed: moderate edema (7 animals), slight edema (3 animals), moderate erythema (8 animals), and slight erythema (2 animals).[8]
Hexyl Salicylate (undiluted)	6 hairless mice	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[8]
Methyl Salicylate (undiluted)	9 rabbits (strain not stated)	Single dermal dose of 5 g/kg	Slight erythema and edema (2 animals) and moderate erythema and edema (7 animals).[9]
Methyl Salicylate (1%, 5%, 10%, 25%, and 100%; for 4 lower concentrations, the vehicle was ethanol/diethyl phthalate 1:1)	6 Albino Mol:Russian rabbits	Semiocclusive patch containing the test substance (0.5 mL) applied for 4 h to the back (2 sites, 2.5 x 2.5 cm area). Patch removal was followed by a 7-day observation period. Reactions scored for up to 14 days after end of exposure.	Undiluted test substance caused slight to well-defined erythema and/or edema in all 6 animals from the 1-h to 72-h grading periods. Reactions had cleared by day 14. The 25% concentration caused very slight erythema in 1 rabbit at the 24-h and 48-h grading periods. Reactions to lower test concentrations were not observed. The test substance was classified as slightly irritating.[46]
Wintergreen oil (contains 80 to 99% Methyl Salicylate)	6 hairless mice and 2 miniature swine	Test substance (20 µl) applied to 5 cm^2 area on back	Flaking, hyperkeratosis, and dry desquamation observed.[9]
Methyl Salicylate	Mice (strain not stated)	Mouse ear swelling test. Test substance (in 4:1 acetone to olive oil) applied in 4-day dosing protocol. The minimal irritating concentration (lowest concentration to produce a % ear swelling significantly greater than the vehicle) was determined.	Minimal irritating concentration was 20%.[72]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.1 mL) applied to 8 cm^2 area on clipped flank (uncovered) daily for 21 days	Minimal skin irritation.[71]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.025 mL) applied for 24 h to 2 cm^2 area on clipped flank (uncovered)	Mild erythema in at least 25% of animals.[71]
Salicylic Acid	3 New Zealand White rabbits (1 male, 2 females).	Test substance (0.5 g in 0.5 mL water) applied for 4 h, under semiocclusive patch, to 2.5 cm x 2.5 cm area of t left flank. Reactions scored at the following intervals after patch removal: 1 h, 24 h, 48 h, 72 h, 7 days, 10 days, and 14 days.	No evidence of skin irritation.[73]
Salicylic Acid	3 New Zealand White rabbits	Test substance (0.5 g, moistened with 0.5 mL water) applied, under semiocclusive patch, for 4 h to 6.25 cm^2 area of skin. Reactions scored for up to 14 days after application.	Non-irritating to the skin of rabbits.[4]
Salicylic Acid (in 8% propylene glycol butyl ether in ethanol). Test concentrations of 2%, 10%, and 25% (corresponding to 40, 200, and 500 mg/kg/day, respectively).	Groups of 6 (3 males, 3 females) New Zealand White rabbits.	14-day dermal toxicity study. Test concentrations were administered topically at a dose of 2 g/kg/day. The control group received topical applications of vehicle only.	Dose-related slight to marked erythema and edema was observed in all dose groups. Desquamation most often observed in the 25% Salicylic Acid group; fissuring (varying degrees) observed in all dose groups. Eschar observed in the 10% and 25% Salicylic Acid groups, and exfoliation also observed in the 25% Salicylic Acid group. Salicylic Acid was irritating to the skin of rabbits.[5]
Salicylic Acid (formulations containing 3.5%, 5%, and 7.5%)	Groups of 6 adult male albino New Zealand rabbits	Formulations applied to concave side of left ears. Distilled water (control) applied to right ears. Macroscopic evaluations performed daily	All 3 formulations caused significant macroscopic alterations (desquamation, inflammatory reaction, and comedogenic effect) when compared to the control.[74]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle)	New Zealand White rabbits (number not stated)	91-day study to evaluate systemic and cutaneous toxicity. Concentration range corresponded to topical doses of 10, 20, 40, or 120 mg/kg Salicylic Acid. Products tested applied for 7 h to intact skin (once daily; dose volume = 2 mL/kg) 5 days per week	Reactions observed at application site included slight to marked erythema, desquamation, fissuring, and edema. The most severe findings, particularly scab formation and desquamation, observed mostly in the highest dose group and during the first 28 days of the study. After 91 days, the severity and frequency of hyperkeratosis, acanthosis, and dermal inflammation were greatest in the high-dose group. Cleansing formulations tested classified as skin irritants.[5]
Alcoholic solutions containing 2%, 2.5%, and 5% Salicylic Acid	Rabbits and guinea pigs (numbers and strains not stated)	Single application of alcoholic solutions containing 2% Salicylic Acid to the skin of rabbits (protocol details not stated). Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs. Each solution applied for 3 h to the skin of guinea pigs twice daily for 4 consecutive days.	Mild to no skin irritation in rabbits. Mild skin irritation in guinea pigs.[4]
2 cleansing formulations containing 0.5% Salicylic Acid	Rabbits (number per study not stated)	Two 91-day studies involving rabbits performed to evaluate cutaneous and systemic toxicity. Undiluted product or product diluted to 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) applied to intact skin. Test article (dose volume of 2 mL/kg; dose = 10 mg/kg) applied to skin 5 times per week (7 h per day). Control rabbits treated with distilled water.	Treatment-related skin changes (varying up to moderate) included transient erythema, edema, atonia, desquamation, and fissuring. Products tested were considered slightly and transiently irritating to the skin when applied undiluted or diluted to a concentration of 50%.[5]
Sodium Salicylate	3 male New Zealand White rabbits	Test substance (0.5 g moistened with 0.5 mL distilled water) applied for 4 h to 6 x 6 cm area in dorsal lumbar region. Site was covered with an occlusive patch during application period. Reactions scored according to method of Draize.	In all 3 rabbits, very slight erythema (barely perceptible) was observed at 1 h, but not at 24 h, 48 h, or 72 h after patch removal; edema was not observed. It was concluded that Sodium Salicylate was non-irritating to the skin of male New Zealand White rabbits. The authors also noted that none of the animals died, and that there was no evidence of systemic toxicity.[43]

Irritation (Human)

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Amyl Salicylate (32% in acetone)	50 adult male subjects	A 15 mm diameter occlusive patch containing 0.05 mL of test substance applied for 48 h. Reactions scored 30 min after patch removal	Skin irritation was not observed.[70]
Ethylhexyl Salicylate (4% in petrolatum)	23 male subjects	48-h closed patch test	Skin irritation was not observed.[7]
Hexyl Salicylate (undiluted)	30 subjects	4-h patch (25 mm Hilltop® chamber) test. Patch contained 0.2 mL of test substance. Reactions read at 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[76]
Hexyl Salicylate (0.3%, 3%, or 30%, in 3:1 diethyl phthalate:ethanol)	56 subjects (15 males, 41 females)	24-h patch test. Test substance (0.3 mL) applied to back using 25 mm Hilltop® chambers. Duplicate patches placed on both sides of spine. Sites evaluated at ~1 h, 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[8]
Methyl Salicylate (30% and 60%)	9 subjects (3 males, 6 females)	25 mL of test substance (in 80% ethanol and 20% deionized water vehicle) pipetted onto the skin (forearm). A PTFE cap was placed over the application site to prevent evaporation. Test substance was applied every 48 h for a total of 6 applications.	Skin irritation was observed at both concentrations.[77]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
12% wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%)	25 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[9]
Methyl Salicylate (8% in petrolatum)	27 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[9]
Shampoo containing 3% Salicylic Acid	Human subjects (number not stated)	Cumulative irritation study. Product applied (as a 4% dilution) continuously under a patch for 12 days.	Potential for skin irritation demonstrated.[5]
Shampoos (prototype or commercial formulations) containing 3% Salicylic Acid and shampoo formulations containing up to 2% Salicylic Acid	Human subjects (number not stated)	Exaggerated use repeated application tests (4 studies) to compare shampoos containing 2% or 3% Salicylic Acid (with a placebo (not defined).	Results indicated no statistically significant differences in combined irritation or transepidermal water loss. Therefore, it was determined that Salicylic Acid at a concentration of 3% in rinse-off shampoo formulations does not appear to be more irritating than the other components of the formulation.[5]
Cream containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to the skin repeatedly for 5 days using occlusive and semi-occlusive patches	Skin irritation was not observed.[5]
Surfactant-based product containing 2% Salicylic Acid (pH of 3.8; diluted concentration not stated)	Human subjects (number not stated)	Applied for 24 h to the skin repeatedly for 12 days using occlusive patches	Mildly irritating.[5]
Surfactant-based product containing 2% Salicylic Acid (pH of 3.8)	Human subjects (number not stated)	Applied for 24 h to the skin repeatedly for 14 days using occlusive patches	Probably mildly irritating under normal use conditions.[5]
Hydroalcoholic gel containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to the skin repeatedly for 21 days using semi-occlusive patches.	Slightly irritating.[5]
Two creams containing 2% Salicylic Acid	Human subjects (number not stated)	Two creams (each in a separate test) applied to the skin of human subjects (number not stated) repeatedly for 21 days using occlusive patches.	One cream classified as non-irritating, and the other classified as moderately irritating.[5]
Cream containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to back in repeated (14 days) open application test.	Did not cause reactions that were different from those induced by the control.[5]
Non-alcoholic lotion containing 2% Salicylic Acid	Human subjects (number not stated)	Home use test. Application for 6 weeks	Mild, transient reactions.[5]
Non-alcoholic cream containing 2% Salicylic Acid	Human subjects (number not stated; 50% had sensitive skin)	Home use test. Application for 6 weeks	Little or no irritation potential.[5]
Non-alcoholic lotions and moisturizers containing 2% Salicylic Acid (pH 2.28)	194 human subjects	Home use test.	Itching, stinging, mild erythema, and burning were reported.[5]
Cream containing 1.5 % Salicylic Acid	Human subjects (number not stated)	Applied for 24 h repeatedly for 21 days using occlusive patches.	Slightly irritating.[5]
Hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82)	Human subjects (number not stated)	Daily applications (2 weeks) to the skin	No skin irritation.[5]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/Peptides	Test Protocol	Results
Sensitization (In Vitro/In Chemico)			
Hexyl Salicylate	In vitro model of dendritic cells	Genomic allergen rapid detection (cell-based alternative to animal testing). Assay based on a biomarker signature comprising 200 genes measured in in vitro model. Assay consistently reports predictive performances of ~90% .	Hexyl Salicylate was predicted to be a skin sensitizer.[78]
Salicylic Acid	Keratinocytes, dendritic cells, and peptides	Integrated testing strategy focusing on the following 3 methods covering the first 3 steps of the adverse outcome pathway: direct peptide reactivity assay (DPRA), keratinocyte activation assay, and dendritic cell line activation assay. Results compared to in vivo data (especially human)	The results for Salicylic Acid were equivocal, but, ultimately, were considered positive results.[79]
Salicylic Acid	Peptides	Allergen-peptide/protein interaction assay, which permits the profiling of all amino acid specific allergen-peptide interactions. Mass spectrometry of target peptides performed	No modifications of peptide-21 or peptide-20 by Salicylic Acid. Non-allergenic Salicylic Acid did not interfere with Cys containing peptide-21 or Cys-free peptide-20.[80]
Sensitization (Animal)			
Hexyl Salicylate	Mice	LLNA. EC3 determined.	A very low EC3 (0.18%) was reported., and thought to have been due to possibly sensitizing impurities.[79]
Hexyl Salicylate	10 inbred Hartley albino guinea pigs	Modified Draize procedure: Induction injections at 0.25%; challenge at 0.1% (injection) and at 5% (topical application). Induction consisted of 4 intradermal injections into flank (0.1 mL each), and challenge (left and right flanks) occurred 14 days later. Second challenge performed 7 days after first	Sensitization was observed after the second challenge.[75]
Hexyl Salicylate	Groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs	Induction phase involved intradermal injection of a sterile water and Freund's complete adjuvant mixture (0.1 mL) into 2.5 cm^2 nuchal area of skin, and 2-h topical application (0.3 mL) of 100% Hexyl Salicylate in 3:1 diethyl phthalate:ethanol using 25 mm Hilltop® chamber patches. Procedure repeated on days 3, 5, 7, 10, and 12. On day 22, topical challenge with 50% Hexyl Salicylate in vehicle and 100% Hexyl Salicylate. Sites observed for up to 3 days post-application	Sensitization was not observed.[8]
Hexyl Salicylate	10 albino Dunkin/Hartley guinea pigs	Magnusson-Kligman maximization test. Induction involved 6 intradermal injections of 1% Hexyl Salicylate to a 2 x 4 cm area in dorsal shoulder region. 7 days later, occlusive patch containing 40% Hexyl Salicylate applied to shoulder for 48 h. At 13 to 14 days post-application of occlusive patch, 24-h challenge (flank) with 8 mm diameter occlusive patch containing 10% Hexyl Salicylate. Three additional challenge applications (on contralateral flanks) at weekly intervals.	Sensitization was not observed.[8]
Methyl Salicylate (50%)	Mice	LLNA	Non-sensitizer.[82]
Methyl Salicylate (0.7 μM)	Mice	LLNA	Number of positive tests / number of total tests was 1 in 4 (25% positive response). Overall, results were classified as negative (non-sensitizer).[81]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate (25% w/v in hydro-alcoholic solution)	20 guinea pigs (strain not stated)	Modified Buehler test protocol. Test substance applied for 6 h once per week for 3 weeks. After a 2-week non-treatment period, animals challenged with same concentration of Salicylic Acid.	No signs of skin sensitization.[4]
Sensitization (Human)			
Butyloctyl Salicylate (undiluted)	Fifty-two male and female subjects	Protocol described as essentially the Draize procedure. A 1" x 1" semiocclusive patch containing the test substance (0.2 mL) applied to upper back (between scapulae) for 24 h, 3 times weekly for total of 9 induction applications. Challenge phase initiated after 2-week non-treatment period. Challenge patch applied for 24 h to a new site (adjacent to induction site). Reactions scored at 24 h and 72 h post-application.	No evidence of a positive skin irritation or sensitization reaction during the study. Test substance was classified as a non-sensitizer.[47]
Hexyl Salicylate (30% in 3:1 diethyl phthalate:ethanol)	103 subjects (29 males and 74 females)	HRIPT. Induction (3 weeks): Occlusive patches (25 mm Hilltop® chamber system) containing test substance (0.3 mL) applied for 24 h to left side of back for 9 applications. Challenge: After 2-week non-treatment period, occlusive challenge patch containing test substance applied for 24 h. Reactions scored at 48 h, 72 h, and 96 h after application.	Neither irritation nor sensitization was observed.[8]
Hexyl Salicylate	Human subjects (number not stated)	Protocol not stated	Human skin sensitization no-observed – effect –level of 35,433 µg/cm^2.[83]
Hexyl Salicylate	Human subjects (number not stated)	Maximization test	No induction was observed at a dose of 20,654 µg/cm^2.
Hexyl Salicylate (3% in petrolatum)	22 subjects	Maximization test. Pre-treatment of test site for 24 h with 5% aqueous sodium lauryl sulfate (SLS), under occlusion. Test substance application, under occlusion, to same site on volar forearm or back for 5 alternate-day-48-h periods. After 10-day non-treatment period, occlusive challenge patches applied for 48 h to 2 new sites (SLS pre-treat- ment and no pre-treatment). Reactions were scored at the time of patch removal and 24 h later.	Neither irritation nor sensitization was observed.[8]
12% Wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum	25 subjects	Maximization test. Induction: Test substance applied, under occlusion, to same site on volar forearm for 5 alternate-day 48-h periods. Prior to initial application only, site pre-treated with 5% aqueous SLS for 24 h. Challenge: After 10- to 14-day non-treatment period, 48-h occlusive challenge patch application (2 patches; pretreatment with 5% SLS for 30 min and no pre-treatment) to new sites. SLS-treated sites served as controls.	Sensitization was not observed.[9]
Methyl Salicylate (8% in petrolatum)	27 subjects	Maximization test. Same protocol, except SLS pre-treatment between patch applications during induction and pre-treatment of challenge site with 10% SLS 1 h before challenge. Reactions read when patches removed and 24 h later	Sensitization was not observed.[9]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate (1.25%)	39 subjects (13 males, 26 females)	HRIPT. Induction: 24-h occlusive patch (1-inch square, at center of 1 x 3 inch adhesive bandage) containing 0.5 mL of test substance). 9 applications to same site over 3-week period. Challenge: On Monday of week 6, 24-h challenge patch containing test substance applied to new site. Reactions scored at 24 h and 72 h after patch removal	Sensitization was not observed.[9]
Formulations containing up to 2% Salicylic Acid	Test populations ranging from 84 to 198 human subjects	Total of 23 human repeated insult patch tests (semi-occlusive or occlusive patches). Patch test protocols not included.	No skin sensitization.[5]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Phototoxicity (In vitro)			
Ethylhexyl Salicylate (0.1 to 316 μg/mL)	Cell suspension of 3T3 fibroblasts (1 x 10^5 cells/mL, 1 x 10^4 cells/well)	3T3 neutral red uptake phototoxicity test. Concentrations applied (in sextuplicate) in 96-well plates. After 1 h of incubation, irradiation with UVA light. Neutral red medium added after second incubation. Photoirritation factor (PIF, ratio of toxicity with and without UV light) was calculated, and value for mean photoeffect (MPE, statistical comparison of dose response curves obtained with and without UV) was determined. PIF > 5 (potential phototoxic hazard). MPE > 0.1 (predicted to be phototoxic). Substance with PIF of > 2 and < 5 or an MPE of > 0.1 and < 0.15 predicted as possibly phototoxic.	PIF = 1.756 (1st run) and 1.043 (2nd run). MPE = 0.109 (1st run) and 0.109 (2nd run). Phototoxicity test results were classified as negative.[88]
Phototoxicity/Photosensitization (Animal)			
Methyl Salicylate (50% in diethyl phthalate)	25 male Dunkin-Hartley guinea pigs, distributed among the following 4 groups: 5 animals irradiated without Methyl Salicylate treatment (Group 1); 5 animals treated with Methyl Salicylate without irradiation (Group 2); 10 animals treated with Methyl Salicylate followed by irradiation (Group 3); and 5 animals treated with vehicle only (Group 4).	Phototoxicity was determined on days 1 and 2. On day 1, 0.1 mL of the test substance was applied for 24 h to the interscapular area (9 cm²) in Groups 2 and 3. Group 4 animals were similarly treated with vehicle (0.1 mL). Group 1 animals were not treated. At 30 min post-treatment, Group 1, 3, and 4 animals were irradiated with an infra-erythematogenic dose (erythema score ≤ 0.5) of UVA (~ 9 J/cm²) and UVB (~ 0.1 J/cm²). The non-irradiated part of the back and flanks were protected from UV light exposure. Cutaneous reactions were scored before and 1, 4, and 24 h after the single application and/or irradiation.[46]	In Group 3 (test substance + irradiation), discrete erythema (grade 1) was observed in 3 of 10 animals at 1 h and 4 h. The erythema observed did not persist to day 2. Questionable erythema (grade 0.5) was observed in a few animals (number not stated), but the reaction was within the range of that reported for Group 4 (irradiated vehicle controls). Based on these results, Methyl Salicylate was not considered phototoxic.[46]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Methyl Salicylate (50% in diethyl phthalate)	Groups of Dunkin-Hartley guinea pigs (same as in preceding photoxicity test)	Photoallergy test involved 6 applications over 8 days. Induction and challenge phases separated by 20-day non-treatment period. Day 1 in preceding phototoxicity test considered first induction application. Five additional applications (from day 2 to day 8) made according to procedure followed on day 1. Cutaneous reactions scored at ~ 24 h after each application and/or irradiation. After 6th application, animals remained free of treatment for 20 days. On day 29 (challenge), test substance (0.1 mL) applied to 2 areas (4 cm^2) on distal part of back that remained untreated during induction (involved Groups 2 and 3). Group 4 animals similarly treated with vehicle (0.1 mL), and Group 1 animals were not treated. At ~ 30 min after treatment, Groups 1, 3, and 4 irradiated on left flank (UVB only) and right flank (UVA only). Cutaneous reactions scored before and 1, 4, and 24 h after challenge application and/or irradiation.	After challenge on day 29, questionable or discrete erythema observed in practically all animals of Groups 1, 3, and 4 at the 1 h and 4 h readings. These reactions persisted in a few animals (number not stated) at the 24 h reading. The authors noted that these slight and transient reactions (similar in controls and treated animals) remained within the range of a local reaction at an infraerythematogenic irradiated dose, and were not attributed to a test substance-related photoallergenic response.[46]
Hexyl Salicylate (undiluted)	12 Skh:hairless-1 mutant mice	Single application of test substance (20 µl/2 cm^2) on back (6 mice). Application followed by exposure to 6 kW long arc xenon lamp (distance = 1 m; intensity = 0.1667 W/m^2) for 40 min and 4 fluorescent blacklight lamps (intensity of 3 W/m^2) for 1 h. Six controls treated with test substance only. Positive control group was treated with 8-methoxy-psoralen in methanol (0.01% w/v). Sites evaluated at 4 h, 24 h, 48 h, 72 h, and 96 h.	No reactions to Hexyl Salicylate + light were observed. Results for 8-methoxypsoralen + light were positive.[8,89]
Hexyl Salicylate (undiluted)	2 miniature swine	Single application of test substance (20 µl/5 cm^2) on back. Irradiation performed for 40 min using same light source and procedure as above.	Phototoxicity was not observed.[8,89]
Hexyl Salicylate (5%, 10%, 50%, or 100%)	2 groups of 5 hairless albino guinea pigs of the Crl:IAF(HA)-hrBR outbred strain	Each concentration (volume = 0.3 mL) applied to dorsal skin along midline using 25 mm Hilltop® chamber. 2 h later, patches removed and sites irradiated for ~ 2.25 h with UVR (2.25 x minimal erythemal dose [MED]) using 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Sites evaluated immediately and 1h and 2 h later, and at 1, 2, and 3 days after application.	Phototoxicity was not observed.[8]
Hexyl Salicylate (50% and 100%, in 3:1 diethyl phthalate:ethanol)	2 groups of 5 Crl:IAF (HA)-hBR outbred albino, hairless guinea pigs	Induction: test substance (0.3 mL, on 25 mm-diameter Hill Top® patch) applied for 2 h to nuchal area of skin (2.5 cm^2). After patch removal, application site exposed for 2.25 h to UVR (2.25 x MED) from 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Procedure repeated (once daily) on days 3, 5, 8, 10, and 12. Challenge: On day 22, patch containing test substance applied for 2 h. Exposure of site to UVR for 2.25 after patch removal. Sites scored at 1 h and 4 h after patch application.	Photoallergy was not observed.[8]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Undiluted wintergreen oil (contains 80 to 99% Methyl Salicylate)	2 miniature swine	Test substance (20 μl/5 cm^2) applied to back. Site exposed for 1 h to UVA light (10 watts/m^2) from fluorescent black light lamps, filtered to limit exposure to long wave UV light only. The negative and positive controls were methanol and 8-methoxy-psoralen (in methanol), respectively	Phototoxicity was not observed.[9]
Phototoxicity (Human)			
Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 diethyl phthalate:ethanol)	56 subjects (41 females, 15 males)	Test substance applied to duplicate patches (25 mm Hilltop® chambers) that were placed on the back (both sides of the spine, 24-h contact period). Each subject had 3 patches containing Hexyl Salicylate (applied to left paraspinal region) and 3 control patches (vehicle and saline controls at non-irradiated sites in right paraspinal region) applied. After removal of patches from the left paraspinal region, the sites were irradiated with 16 J/cm^2 of UVA for 10 min, and, then, with UVB (0.75 MED). Sites evaluated at 1 h, 24 h, 48 h, and 72 h after irradiation	No reactions were observed.[8]

REFERENCES

References

1. Andersen FA (ed). Safety assessment of Salicylic Acid, Butyloctyl Saicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate. *International Journal of Toxicology*. 2003;22(3):1-108.

2. Fiume, MM, Heldreth, B, Bergfeld, W, Belsito, D, Hill, R, Klaassen, C, Liebler, D, Marks Jr., J, Shank, R, Slaga, T, Snyder, P, and Andersen, F. Safety assessment of ethanolamine and ethanolamine salts as used in cosmetics. *International Journal of Toxicology*. 2015;34(2):84S-98S.

3. Nikitakis, J. and Lange B. International Cosmetic Ingredient Dictionary and Handbook Online Version (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC. Last Updated 2018. Date Accessed 3-6-2017.

4. Scientific Committee on Consumer Safety (SCCS). Opinion on salicylic acid (CAS 69-72-7). Submission 1. Adopted by written procedure on December 21, 2018. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_223.pdf. Last Updated 2018. Date Accessed 1-7-2019.

5. Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers. http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out170_en.pdf. Last Updated 2002. Date Accessed 10-31-2018.

6. The Metabolomics Innovation Center (TMIC). Metabocard for salicin (HMDB0003546). http://www.hmdb.ca/metabolites/HMDB0003546. Last Updated 2019. Date Accessed 3-11-2019.

7. Lapczynski, A., McGinty, D, Jones, L, Letizia, CS, and Api, AM. Fragrance material review on ethyl hexyl salicylate. *Food Chem Toxicol.*. 2007;45(7):S393-S396.

8. Lapczynski, A., Jones, L, McGinty, D, Bhatia, S, Letizia, CS, and Api, AM. Review. Fragrance material review on hexyl salicylate. *Food and Chemical Toxicology*. 2007;45:S410-S417.

9. Lapczynski, A, Jones, L, McGinty, D, Bhatia, SP, Letzia, CS, and Api, AM. Review. Fragrance material review on methyl salicylate. *Food and Chemical Toxicology*. 2007;45:S428-S452.

10. PerkinElmer Informatics. ChemDraw® 17. 2017.

11. Advanced Chemistry Development Labs (ACD Labs). Properties estimated using ACD Labs software. V11.02. 2019.

12. Chemical Abstracts Service (CAS). Scifinder®. Substance identifier: Key properties of Salicylic Acid, Hexyldodecyl Salicylic Acid, Sodium Salicylate, Tridecyl Salicylate, and Amyl Salicylate. http://www.cas.org. Last Updated 2019. Date Accessed 1-7-2019.

13. Freeman, A. and Haller HL. Preparation of amyl salicylates. *Journal of the American Chemical Society*. 1938;60:2274-2275.

14. Hua, Y and Rong-xuan, MA. Synthesis of n-amyl salicylate catalyzed by sodium hydrogen sulfate. *Huaxue Yu Shengwu Gongcheng*. 2009;26(7):29-31.

15. United States Pharmacopoeial Convention. The United States Pharmacopoeia (USP). 32nd *ed*. Rockville, Maryland: The United States Pharmacopoeial Convention, 2009.

16. United States Pharmacopoeial Convention. The National Formulary (NF). 27th *ed*. Rockville, Maryland: The United States Pharmacopoeial Convention, 2009.

17. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD, 2019.

18. Personal Care Products Council. Concentration of Use by FDA Product Category: Salicylates. Unpublished data submitted by the Personal Care Products Council on 6-11-2018. 2018. pp.1-5.

19. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104. PM:21669261.

20. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 20200. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

21. Rothe H. Special aspects of cosmetic spray evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C. 2011.

22. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;14(11):24-27. http://www.spraytechnology.com/index.mv?screen=backissues.

23. Aylott RI, Byrne GA, Middleton, J, and Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci*. 1979;1(3):177-186. PM:19467066.

24. Russell RS, Merz RD, Sherman WT, and Sivertson JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122. PM:478394.

25. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic Powder Exposure.

26. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2018. Date Accessed 10-24-2018.

27. International Fragrance Association (IFRA). Sandards library. Hexyl Salicylate limits in the finished product (%). http://www.ifraorg.org/en-us/standards-library. Last Updated 2007. Date Accessed 11-30-2018.

28. Davis, J. E. Selected Topics: Toxicology. Are one or two dangerous? Methyl salicylate exposure in toddlers. *The Journal of Emergency Medicine*. 2007;32(1):63-69.

29. Banti, C. N, Giannoulis, AD, Kourkoumelis, N, Owczarzak, AM, Kubicki, M, and Hadjikakou, SK. Silver (I) compounds of the anti-inflammatory agents salicylic acid and p-hydroxyl-benzoic acid which modulate cell function. *Journal of Inorganic Biochemistry*. 2015;142:132-144.

30. European Chemicals Agency (ECHA). Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) Dossier. Ethylhexyl Salicylate. https://echa.europa.eu/registration-dossier/-/registered-dossier/14203. Last Updated 2018. Date Accessed 10-25-2018.

31. Chatelain, E, Gabard, B, and Surber, C. Skin penetration and sun protection factor of five UV filters: Effect of the vehicle. *Skin Pharmacol.Appl.Skin Physiol.* 2003;16:28-35.

32. Cross, S. E, Megwa, SA, Benson, HAE, and Roberts, MS. Self promotion of deep tissue penetration and distribution of methylsalicylate after topical application. *Pharmaceutical Research*. 1999;16(3):427-433.

33. Moody, R. P, Akram, M, Dickson, E, and Chu, I. In vitro dermal absorption of methyl salicylate, ethyl parathion, and malathion: First responder safety. *Journal of Applied Toxicology and Environmental Health, Part A*. 2007;70(12):985-999.

34. Riviere, J. E, Smith, CE, Budsaba, K, Brooks, JD, Olajos, EJ, Salem, H, and Monteiro-Riviere, NA. Use of methyl salicylate as a stimulant to predict the percutaneous absorption of sulfur mustard. *The Toxicologist*. 2000;54:151-152.

35. Riviere, J. E, Smith, CE, Budsaba, K, Brooks, JD, Olajos, EJ, Salem, H, and Monteiro-Riviere, NA. Use of methyl salicylate as a stimulant to predict the percutaneous absorption of sulfur mustard. *Journal of Applied Toxicology*. 2001;21:91-99.

36. Higo, N, Sato, S, Irie, T, and Uekama, K. Percutaneous penetration and metabolism of salicylic acid derivatives across hairless mouse skin in diffusion cell in vitro. *STP Pharma Sciences*. 1995;5:302-308.

37. Duncan, E. J. S., Brown, A, undy, P, awyer, TW, amilton, M, ill, I, and onley, JD. Site-specific percutaneous absorption of methyl salicylate and VX in domestic swine. *Journal of Applied Toxicology*. 2002;22:141-148.

38. Hayden, C. G, Roberts, MS, and Benson, HA. Systemic absorption of sunscreen after topical application. *Lancet*. 1997;350:863-864.

39. Martin, D, Valdez, J, , BJ, and Mayersohn, M. Dermal absorption of camphor, menthol, and methyl salicylate in humans. *J.Clin.Pharmacol.* 2004;44:1151-1157.

40. Watkinson, A. C, Brain, KR, Walters, KA, and Hadgraft, J. Prediction of the percutaneous penetration of ultraviolet filters used in sunscreen formulations. *Internatinoal Journal of Cosmetic Science.* 1992;14:265-275.

41. Shintaku, K, Arima, Y, Dan, Y, Takeda, T, Kogushi, K, Tsujimoto, M, Nagata, H, Satoh, S, Tsukimori, K, Nakano, H, Hori, S, Ohtani, H, and Sawada, Y. Kinetic analysis of the transport of salicylic acid, a nonsteroidal anti-inflammatory drug, across human placenta. *Drug Metab.Dispos.* 2018;35(5):772-778.

42. Wolowich, W. R, Hadley, CM, Kelley, MT, Walson, PD, and Casavant, MJ. Plasma salicylate from methyl salicylate cream compared to oil of wintergreen. *Journal of Toxicology: Clinical Toxicology.* 2003;41(4):355-358.

43. European Chemicals Agency (ECHA). Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) Dossier. Sodium Salicylate. https://echa.europa.eu/registration-dossier/-/registered-dossier/13593. Last Updated 2018. Date Accessed 10-26-2018.

44. Ohsumi, T, Kuroki, K, Kimura, T, and Murakami, Y. A study on acute toxicities of essential oils used in endodontic treatment. *Journal Kyushu Dental Society.* 1984;38:1064-1071.

45. Ojiambo, H. P. Hindlimb metabolism in dogs intoxicated with methyl salicylate. *East African Medical Journal.* 1972;48:476-481.

46. European Chemicals Agency (ECHA). Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) Dossier. Methyl Salicylate. https://echa.europa.eu/registration-dossier/-/registered-dossier/2227. Last Updated 2018. Date Accessed 10-27-2018.

47. European Chemicals Agency (ECHA). Registration, Evaluation, and Authorization of Chemicals (REACH) Dossier. 2-hydroxybenzoic acid 2-butyloctyl ester (Butyloctyl Salicylate). https://echa.europa.eu/registration-dossier/-/registered-dossier/25791. Last Updated 2018. Date Accessed 10-25-2018.

48. National Toxicology Program (NTP). Methyl salicylate: Reproduction and fertility assessment in CD-1 mice when administered by gavage. NTP-84-156; PB84-241140. 1984.

49. Fukayama, M. Y., Easterday, OD, Serafino, PA, Renskers, KJ, North-Root, H, and Schrankel, KR. Subchronic inhalation studies of complex fragrance mixtures in rats and hamsters. *Toxicology Letters.* 1999;111:175-187.

50. Singh, G, Sinha, N, and Sinnollareddy MG. Role of apoptosis in mediating salicylic acid-induced teratogenesis in vitro. *Toxicol.Mech.Methods.* 2009;19(2):161-168.

51. Karabulut, A. K. Ulger H. and Pratten M. K. Protection by free radical oxygen scavenging enzymes against salicylate-induced malformations in vitro. *Toxicology In Vitro.* 2000;(14):297-307.

52. Foulon, O. Jaussely C. Repetto M. Urtizberea M. and Blacker A. M. Postnatal evolution of supernumerary ribs in rats after a single administration of sodium salicylate. *J.Appl.Toxicol.* 2000;20:205-209.

53. Wéry, N. Foulon O. Blacker A. Pickard J. J. and Gofflot F. Vertebral malformations induced by sodium salicylate correlate with shifts in expression domains of *Hox* genes. *Reproductive Toxicology.* 2005;20:39-45.

54. Zhang, Q. Ye X. Wang L. Peng B. Zhang Y. Bao J. Li. W. Wei J. Wang A. Jin H. et al. Embryo-fetal developmental toxicity of honokiol microemulsion intravenously administered to pregnant rats. *Regulatory Toxicology and Pharmacology.* 2016;74:117-122.

55. Lam, J. Polifka J. E. and Dohil M. A. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J.Am.Acad.Dermatol.* 2008;59:295-315.

56. Patel, V. M. Schwartz R. A. and Clark L. W. Safety of topical dermatologic medications in pregnancy. *Journal of Drugs in Dermatology.* 2016;15(7):830-834.

57. Fung, W, Orak, D, Re, T, and Haughey, D. Relative bioavailability of salicylic acid following dermal application of a 30% salicylic acid skin peel preparation. *J.Pharm.Sci.* 2008;97(3):1325-1328.

58. Moore, TJ, Joseph, M, Allen, B, and Coury, LJr. Enzymatically amplified voltammetric sensor for microliter sample volumes of salicylate. *Anal.Chem.* 1995;67:1896-1902.

59. Tietz, N. W. Textbook of Clinical Chemistry. W.B.Saunders Company, 1986.

60. Labib, R, Bury, D, Boisleve, F, Eichenbaum, G, Girard, S, Naciff, J, Leal, M, and Wong. A kinetic-based safety assessment of consumer exposure to salicylic acid from cosmetic products demonstrates no evidence of a health risk from developmental toxicity. *Regul.Toxicol.Pharmacol.* 2018;94:245-251.

61. International Program on Chemical Safety (IPCS). Chemical-specific adjustment factors for interspecies differences and human variability. IPCS harmonization of approaches to the risk assessment from the exposure to chemicals. World Health Organization (WHO), Geneva, Switzerland. 2005.

62. Madan, R. K. and Levitt J. A review of toxicity from topical salicylic acid preparations. *J.Am.Acad.Dermatol.* 2014;70:788-792.

63. European Commission. The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation. 9th revision. 2015.

64. Davis, DA, Kraus, A, Thompson, G, Olerich, M, and Odio, M. Percutaneous absorption of salicylic acid after repeated (14-day) in vivo administration to normal, acnegenic or aged human skin. *J.Pharm.Sci.* 1997;86(8):896-899.

65. National Toxicology Program (NTP). NTP technical report on the photocarcinogenesis study of glycolic acid and salicylic acid (CAS Nos. 79-14-1 and 69-72-7) in SKH-1 mice (simulated solar light and topical application study). NTP TR 524. NIH Publication No. 07-4472. 2007.

66. Hong, H, Rua, D, Sakkiah, S, Selvaraj, C, Ge, W, and Tong, W. Consensus modeling for prediction of estrogenic activity of ingredients commonly used in sunscreen products. *Int.J.Environ.Res.Public Health*. 2016;13(10):958

67. Miller, D, Wheals, BB, Beresford, N, and Sumpter, JP. Estrogenic activity of phenolic additives determined by an in vitro yeast bioassay. *Environmental Health Perspectives*. 2001;109(2):133-138.

68. De Jong, W. H, Arts, JHE, De Klerk, A, Schijf, MA, Ezendam, J, Kuper, CF, and Loveren, HV. Contact and resiratory sensitizers can be identified by cytokine profiles following inhalation exposure. *Toxicology*. 2009;261:103-111.

69. Cassanoa, N. Alessandrini G. Mastrolonardoa M. and Vena G. A. Review article. Peeling agents: toxicological and allergological aspects. *Journal of the European Academy of Dermatology and Venereology*. 1999;13:14-23.

70. Motoyoshi, K. Toyoshima Y. Sato M. and Yoshimura M. Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guina pig, rat, miniature swine and man. *Cosmetic and Toiletries*. 1979;94:41-48.

71. Klecak, G. Geleick H. and Frey J. R. Screening of fragrance materials for allergenicity in ghe guinea pig. I. Comparison of four testing methods. *Journal of the Society of Cosmetic Chemists Japan*. 1977;28:53-64.

72. Howell, M. D. Manetz T. S. and Meade B. J. Comparison of murine assays for the identification of chemical sensitizers. *Toxicology Methods*. 2000;10(1):1-15.

73. European Chemicals Agency (ECHA). Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) Dossier. Salicylic Acid. https://echa.europa.eu/registration-dossier/-/registered-dossier/14544. Last Updated 2018. Date Accessed 10-28-2018.

74. Truite, C. V. R. Philippsen G. S. Ueda-Nakamura T. Natali M. R. M. Filho B. P. D. Bento A. C. Baesso M. L. and Nakamura C. V. Percutaneous penetration, malanin activation, and toxicity evaluation of a phytotherapic formulation for vitiligo therapeutic. *Photochemistry and Photobiology*. 2007;83:1529-1536.

75. Sharp, D. W. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. *Toxicology*. 1978;9:261-271.

76. Basketter, D. A. York M. McFadden J. P. and Robinson M. K. Determination of skin irritation potential in the human 4-h patch test. *Contact Dermatitis*. 2004;51:1-4.

77. Green, B. G. and Shafffer G. S. Psychophysical assessment of the chemical irritability of human skin. *Journal of the Society of Cosmetic Chemists Japan*. 1992;43:131-147.

78. Forreryda, A. Norinder U. Lindberg T. and Lindstedt M. Predicting skin sensitizers with confidence - Using conformal prediction to determine applicability domain of GARD. *Toxicology In Vitro*. 2018;48:179-187.

79. Cloueta, E. Kersine-Romer S. and Ferrata P. Comparison and validation of an in vitro skin sensitization strategy using a data set of 33 chemical references. *Toxicology In Vitro*. 2017;45:374-385.

80. Dietz, L. Kinzebach S. Ohnesorge S. Franke B. Goette I. Koenig-Gressel D. and Thierse H. Proteomic allergen--peptide/protein interaction assay for the identification of human skin sensitizers. *Toxicology In Vitro*. 2013;27:1157-1162.

81. Ahmeda, S. S. Wang N. Fielding M. Kerry A. Dickinson I. Munuswamy R. Kimberc I. and Dickinson A. M. An in vitro human skin test for assessing sensitization potential. *J.Appl.Toxicol.* 2016;36:669-684.

82. Hou, F. Xing C. Li B. Cheng J. Chen W. and Zhang M. Application of BALB/c mouse in the local lymph node assay: BrdU-ELISA fo the prediction of the skin sensitizing potential of chemicals. *Journal of Pharmacological and Toxicological Methods*. 2015;72:53-58.

83. Basketter, D. A. Alepee N. Ashikaga T. Barroso J. Gilmour N. Goebel C. Hibatallah J. Hoffmann S. Kern P. Martinozzi-Teissier S. Maxwell G. Reisinger K. Sakaguchi H. Schepky A. Tailhardat M. and Templier M. Categorization of chemicals according to their relative human skin sensitizing potency. *Dermatitis*. 2014;25:11-21.

84. Cronin, M. T. D. and Basketter D. A. Multivariate QSAR analysis of a skin sensitization database. *SAR and QSAR in Environmental Research*. 1994;2(3):159-179.

85. Dimitrov, S. D. Low L. K. Patlewicz G. Y. Kern P. S. Dimitrova G. D. Comber M. H. I. Phillips R. D. Niemela J. Bailey P. T. and Mekenyan O. G. Skin sensitization: Modeling based on skin metabolism simulation and formation of protein conjugates. *International Journal of Toxicology*. 2005;24:189-204.

86. Hostynek, J. J and Magee P. S. Fragrance allergens: Classification and rankings by QSAR. *Toxicology In Vitro*. 1997;11:377-384.

87. International Fragrance Association (IFRA). Code of Practice, Standard on hexyl salicylate. Brussels. 2007.

88. Gaspar, L. R. Tharmann J. Campos P. and Liebsch M. Skin phototoxicity of cosmetic formulations containing photounstable and photostable UV-filters and vitamin A palmitate. *Toxicology In Vitro*. 2013;27:418-425.

89. Forbes, P. D. Urbach F. and Davies R. E. Phototoxicity testing of fragrance raw materials. *Food and Cosmetics Toxicology*. 1977;15:55-60.

90. Kandorova, H. Letasiova S. Adriaens E. Guest R. Willoughby J. A. Sr. Drzewiecka A. Gruszka K. Alépée N. Verstraelen S. and Rompay A. R. V. CON4EI: EpiocularTM eye irritation test (EpiOcular™ EIT)for hazard identification and labelling of eye irritating chemicals. *Toxicology In Vitro*. 2017;49:21-33.

91. Carpenter, C. P. and Smyth H. F. Chemical burns of the rabbit cornea. *American Journal of Ophthalmology*. 1946;29:1363-1372.

92. Frosch, P. J. Pilz b. Andersen K. E. Burrows D. Camarasa J. G. Dooms-Goossens A. Ducombs G. Fuchs T. Hannuksela M. Lachapelle J. M. et al. Patch testing with fragrances: results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis*. 1995;33(5):333-342.

93. Frosch, P. J. Johansen J. D. Menne T. Pirker C. Rastogi S. C. Andersen E. Bruze M. Goossens A. Lepoittevin J. P. and White I. R. Further important sensitizers in patients sensitive to fragrances. I. Reactivity to 14 frequently used chemicals. *Contact Dermatitis*. 2002;47:78-85.

94. Larsen, W. Nakayama H. Fischer T. Elsner P. Frosch P. Burrows D. Jordan W. Shaw S. Wilkinson J. Marks J. Sugawara M. Nethercott M. and Nethercott J. Fragrance contact dermtitis - a worldwide multicenter investigation (Part III). *Contact Dermatitis*. 2002;46:141-144.

95. Bell, A. J. and Duggin G. Case report. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. *Emergency Medicine*. 2002;14:188-190.

96. Norsworthy, J, Bhatti, Z, and George, T. Topical salicylic acid hypersensitivity. *Am.J.Ther.* 2018;25(5):e568-e569.

97. Mortz, C. G., Thormann, H, Goossens, A, and Andersen, KE. Allergic contact dermatitis from ethylhexyl salicylate and other salicylates. *Dermatitis*. 2010;21(2):E7-E10.

98. Miralles, J. C. Escudero A. Carbonell A. Martinez A. Fernández E. and Cardona P. Allergic contact dermatitis from ethylhexyl salicylate. *J.Investig.Allergol.Clin.Immunol.* 2015;25(1):55-82.

99.   Zheng, Y, Yin, S, Xia, Y, Chen, J, Ye, C, Zeng, Q, and Lai, W. Efficacy and safety of 2% supramolecular salicylic acid compared with 5% benzoyl peroxide/0.1% adapalene in the acne treatment: A randomized, splkit-face, open-label, single-center study. *Cutan.Ocul.Toxicol.* 2018;3:1-21.

100.   Belsito, D, Bickers, D, , BM, Calow, P, Greim, H, Hanifin, JH, Rogers, AE, Saurat, JH, Sipes, IG, and Tagami, H. A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients. *Food and Chemical Toxicology*. 2007;45(1S1):S318-S361.